ADDITUDE
Strategies & Support for ADHD and Beyond

The Surprising Association Between ADHD & Inflammation

February 27, 2025
Podcast # 545

ADHD expert webinars
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ADDITUDE
Strategies & Support for ADHD and Beyond

Meet today's expert speaker:

James Kustow, BMedSci, BMBS, MRCPsych

Dr. James Kustow is a leading London-based Consultant Psychiatrist and a trained integrative psychotherapist, working in one of the few specialist NHS adult ADHD services in the capital.

Dr. Kustow also has a busy private practice, and is the Medical Director of The Grove Practice, an internationally respected mental health training provider.

Dr. Kustow has developed a specialist clinical expertise working with adult ADHD, both in terms of its diagnosis and medical management, but additionally in the development of comprehensive psychosocial interventions.

He is the author of *How to Thrive with Adult ADHD*.

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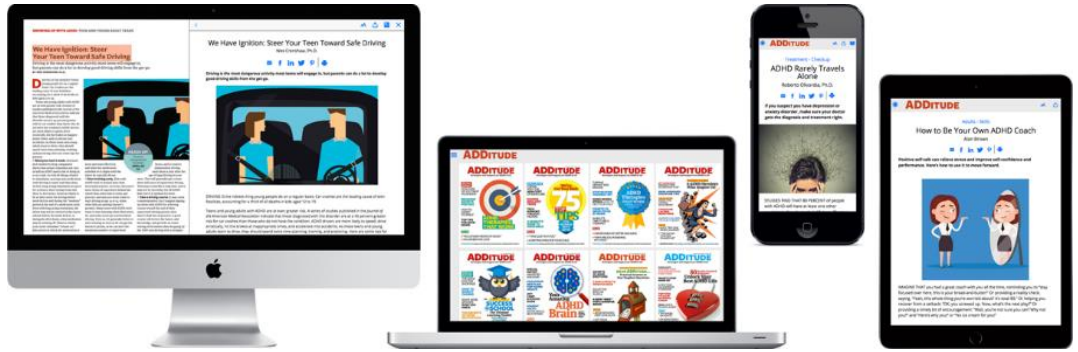

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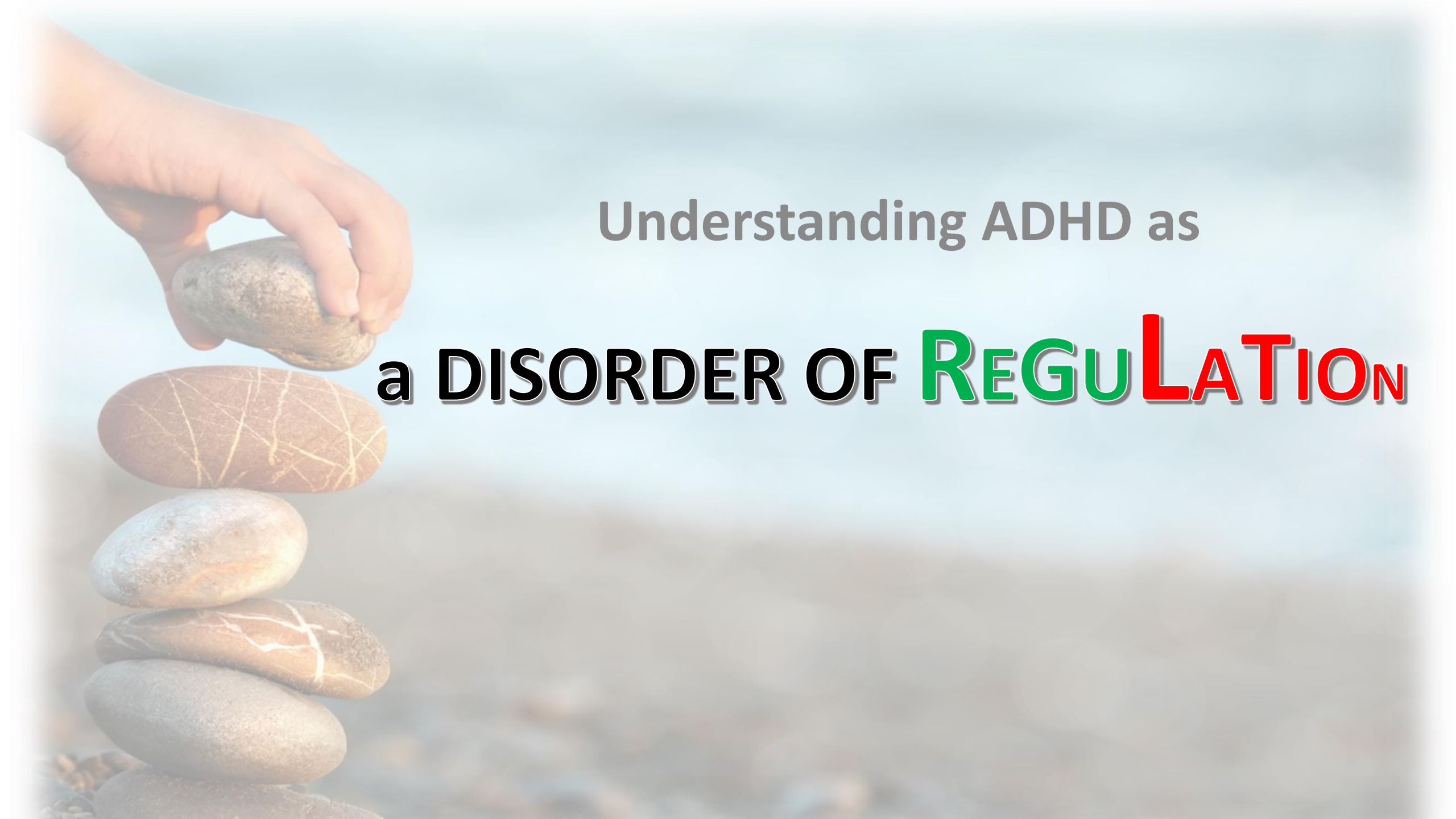
- Speaker fees: *Eli Lilly, Janssen-Cilag, Shire,* and *Flynn Pharma*
- Consultancy services: *Eli Lilly, Shire,* and *Flynn Pharma*
- I am a member of *UKAAN's* Executive board and serve as *UKAAN's* Director of Education
- I am a co-author of the *Handbook for the Diagnosis and Treatment of ADHD in Adults* (Springer Healthcare)
- I have a private practice in London (UK)
- I am the author of *How to Thrive with Adult ADHD* (Penguin)

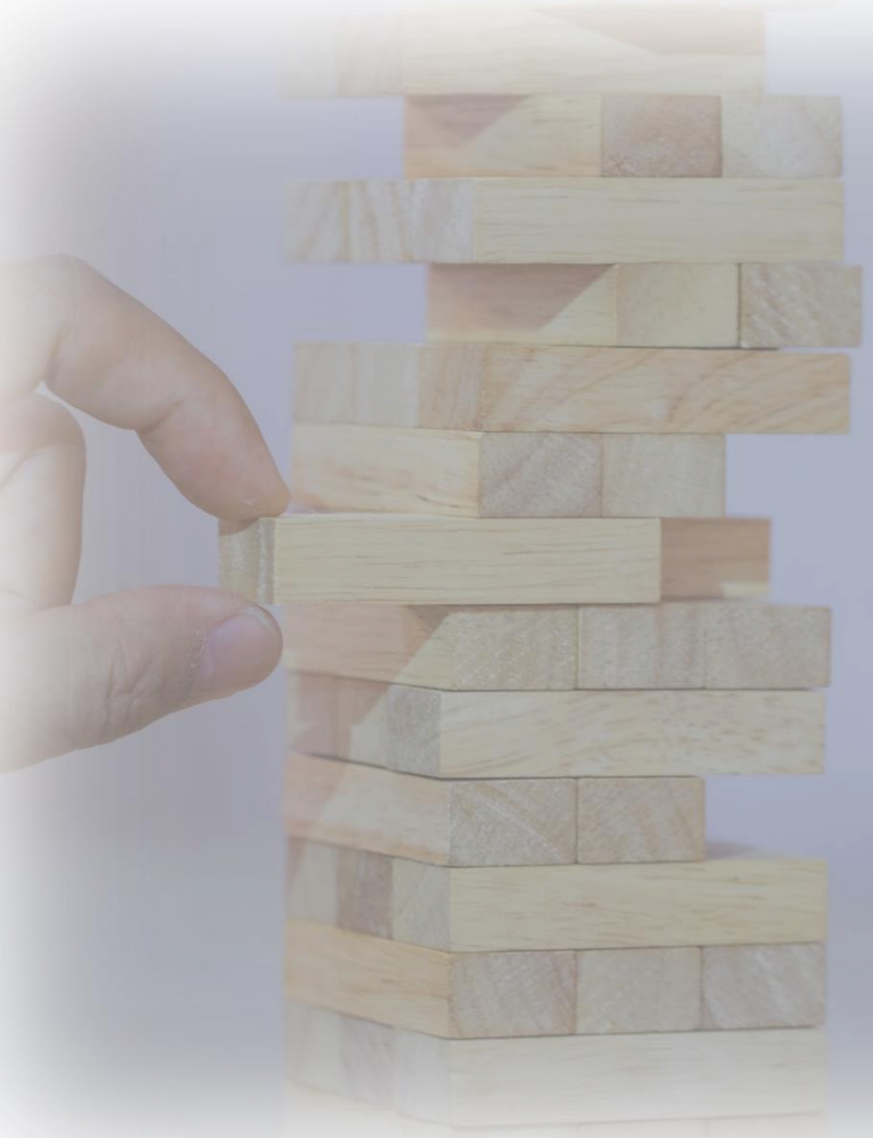
- To **widen the lens** around ADHD, and bring the focus more to the body
- To explore the **somatic** (or physical health) **comorbidity** (overlap) in ADHD
- To introduce my **10-point Neuroinflammatory Hypothesis of ADHD**, and provide an overview of the inflammatory presentations that have established links to ADHD
- To consider the relationship between **ADHD and joint hypermobility**, and explain how this may provide the key link with inflammation (possibly via **mast cell activation disease**)
- To introduce the **Somatic Super Syndrome (3S)** model, and its "neuropsychiatric signature"



Understanding ADHD as

a DISORDER OF REGULATION

Beyond DSM.....



The ***10 Domains of Dysregulation model*** captures **the lived-experience** (and the science) of ADHD

- Associated with each of the 10 domains are a set of **1st level features**

  Symptoms or features that result from the dysregulation of that domain

- There are a range of (non-domain specific) **2nd level features**, divided into:

  (1) longer-term consequences or ***adverse*** *outcomes*

  (2) potentially ***adaptive*** *features linked to ADHD*

The *10 Domains of Dysregulation* Model

Domain 1: Attention

Domain 2: Activity

Domain 3: Impulse

Domain 4: Emotion

THE CORE 4

Domain 5: Pleasure seeking / reward

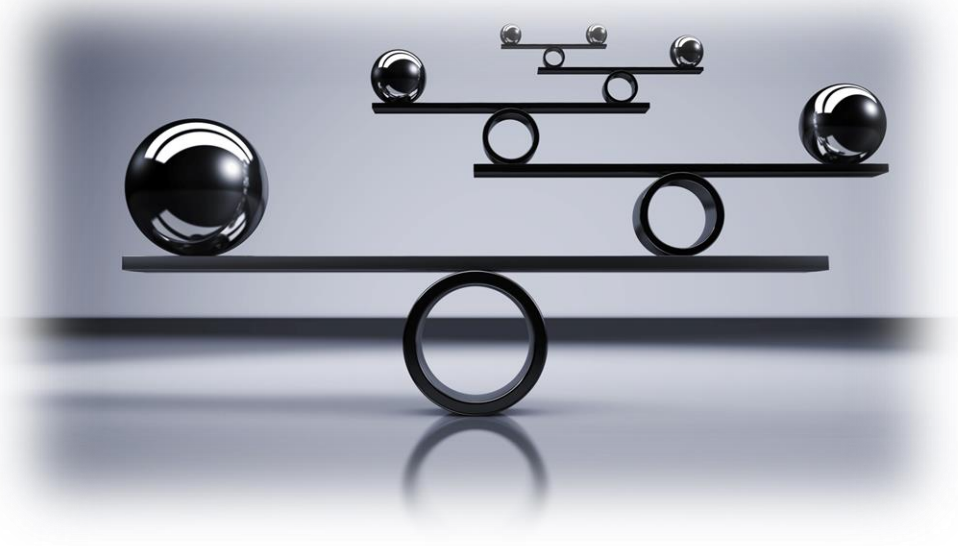
Domain 6: Sensory processing

Domain 7: Time appraisal

Domain 8: Sleep-wake (circadian) rhythm

Domain 9: Immune function (& inflammation)

Domain 10: Energy expenditure & arousal



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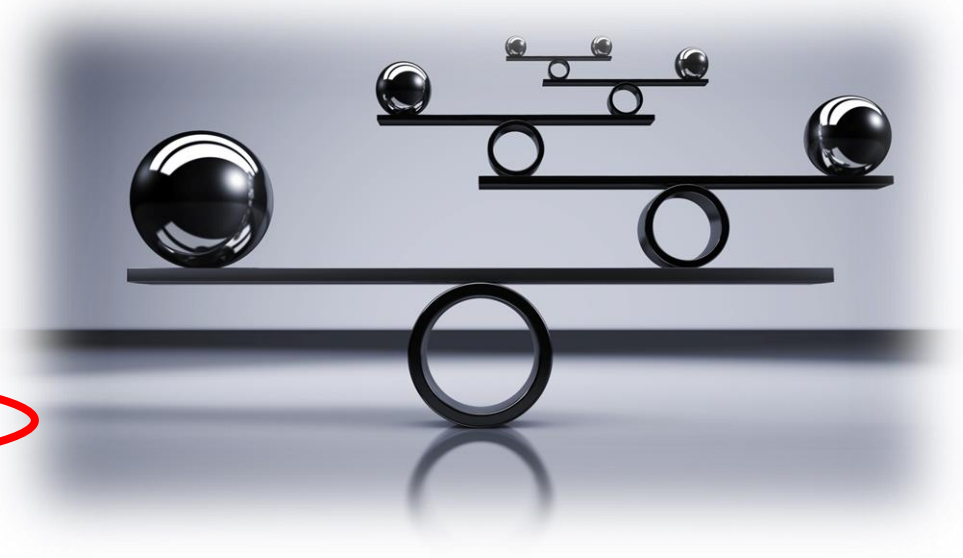


The Inflammatory Hypothesis of ADHD

10 findings that support the association between inflammation and ADHD:

1. ADHD commonly **coexists with inflammatory conditions**, including allergies and autoimmune disorders.

2. Studies consistently show **elevated pro-inflammatory markers** in individuals with ADHD.

3. **Premature birth, low birth weight, and neonatal infections** increase the risk of ADHD.

4. **Maternal inflammation** from allergies, autoimmunity, or metabolic dysfunction (e.g., obesity) raises ADHD risk via fetal neuroinflammatory pathways.

5. **Gut dysbiosis**, associated with inflammation, influences neuropsychiatric disorders, including ADHD.

The Inflammatory Hypothesis of ADHD
(continued)

6. **Methylphenidate may reduce inflammation** in ADHD, though findings are inconsistent.

7. **Animal studies** suggest links between ADHD-related traits and inflammation.

8. **Food allergies and intolerances** (IgE and non-IgE) contribute to gut and systemic inflammation, potentially triggering ADHD, possibly via microbiome effects.
   [Note: Some studies, including a 2017 meta-analysis, have not demonstrated an association between ADHD and food allergy, but distinction between allergy and intolerance may explain this finding.]

9. Genetic studies show **variants in inflammation-related genes** are associated with ADHD.

10. **Indirect evidence:** Vitamin D lower in ADHD; iron-deficiency (& low ferritin) more common in ADHD; ADHD children have lower PUFA levels, and supplementation with PUFAs is effective.

Inflammation and ADHD

'Kustow's 10-point Neuroinflammatory Hypothesis of ADHD'

10 clusters of findings that support the association between inflammation and ADHD:

1. **Established comorbidity between ADHD and inflammatory presentations** including allergy, atopy and autoimmune disorders (Chen et al. 2018, van der Schans et al. 2017; Miyazaki et al. 2017; Cortese et al. 2018), infections e.g. Covid 19, (Ameratunga et al. 2023), Shigella (Merzon et al. 2021), urinary infections in children (Mahajani et al. 2021), and a range of gastrointestinal (especially salmonella), respiratory tract and urinary tract infections (Merzon et al. 2023); and immune deficiency e.g. Selective Immunoglobulin A Deficiency, which is linked to mucosal infection (Merzon et al. 2024).

2. **Raised pro-inflammatory factors / markers** (including cytokines and chemokines e.g. IL2, IL6, IL-1Beta, interferon gamma and TNF alpha; autoantibodies e.g. anti-Purkinje, anti-basal ganglia and anti-dopamine transporter; eosinophils and IgE) have been shown to be associated with ADHD (Ribasés et al. 2008; O'Shea et al. 2014; Anand et al. 2017; Darwish et al. 2019; Kozlowska et al. 2019; Donfrancesco et al. 2020;), increase the risk of ADHD, and worsen ADHD (Cortese and Vincenzi, 2012; Cortese et al. 2019).
[*Note: there are also negative studies, e.g. lack of association between maternal CRP levels and the risk of ADHD in offspring* (Chudal et al. 2020).]

Comorbidity Between ADHD & Inflammatory Conditions

1. Allergy & Atopy

- **Allergic rhinitis** (Chen et al. 2018; van der Schans et al. 2017; Miyazaki et al. 2017; Cortese et al. 2018)
- **Asthma** (Cortese et al. 2018)
- **Eczema & Atopic dermatitis** (Akmatov et al. 2021)

2. Autoimmune Disorders

- **Psoriasis** (Hegvik et al. 2018) and **Type 1 diabetes** (Kapellen et al. 2016)
- **Ankylosing spondylitis, ulcerative colitis,** and **autoimmune thyroid disease** (Chen et al. 2017)
- **PANS / PANDAS** (Pediatric Autoimmune Neuropsychiatric Disorders)

3. Infections

- **COVID-19** (Ameratunga et al. 2023)
- **Gastrointestinal, respiratory,** and **urinary tract infections** (in children) (Merzon et al. 2021; 2023; Mahajani et al. 2021)
- **Sexually transmitted infections** (Chen et al. 2018c)

4. Immune Deficiency & ADHD

- **Selective IgA Deficiency** – linked to increased mucosal infections (Merzon et al. 2024)

Comorbidity Between ADHD & Inflammatory Conditions

5. Metabolic Conditions

- **Obesity** (Chen et al. 2018a; Cortese 2016)
- **Metabolic syndrome** (Akmatov et al. 2021)
- **Type 2 diabetes** (Chen et al. 2018b)

6. Neurological & Sleep-Related Conditions

- **Epilepsy** (Bertelsen et al. 2016; Chou et al. 2013; Brikell et al. 2018)
- **Sleep-disordered breathing** (Sedky et al. 2014)
- **Migraine** (Arruda et al. 2020)

7. Connective Tissue, Pain & Fatigue Disorders

- **Hypermobility syndromes & connective tissue disorders** (Cederlöf et al. 2016; Csecs et al. 2020)
- **Fibromyalgia** – 44% of fibromyalgia (FMS) patients have ADHD (van Rensburg et al. 2018)
- **Chronic pain** – ADHD symptoms correlate with higher pain sensitivity (Stickley et al. 2016)
- **Chronic fatigue syndrome** – 30% prevalence of childhood ADHD, 21% persist (Saez-Francas et al. 2012)

Inflammatory Markers in ADHD

1. Elevated Pro-Inflammatory Factors (blood levels)

- Cytokines & Chemokines: IL-2, IL-6, IL-1β, interferon-γ, TNF-α
- Autoantibodies: Anti-Purkinje, anti-basal ganglia, anti-dopamine transporter
- Eosinophils & IgE elevation

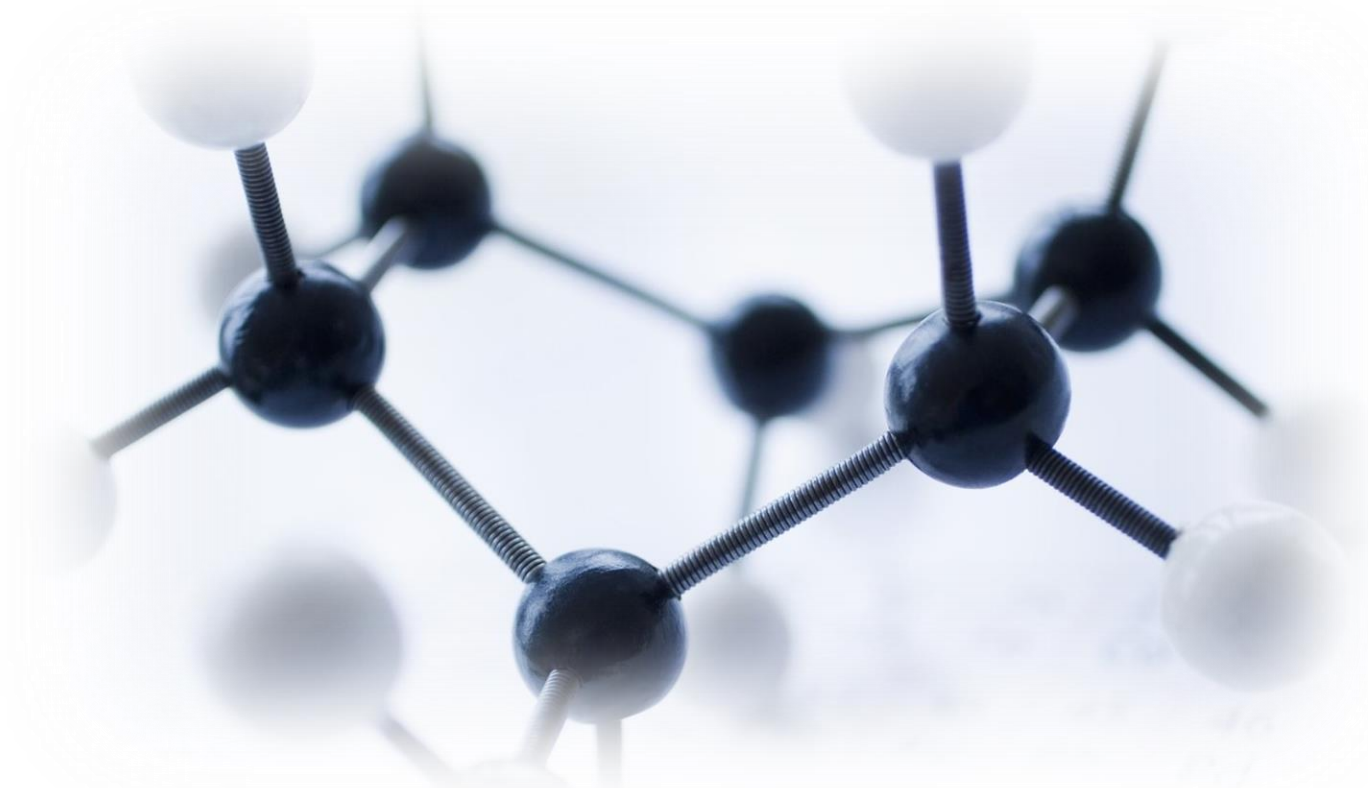
(Ribasés et al. 2008; O'Shea et al. 2014; Anand et al. 2017; Darwish et al. 2019; Kozlowska et al. 2019; Donfrancesco et al. 2020)

2. ADHD & Immune System Dysfunction

- Higher inflammatory load increases risk and severity of ADHD (Cortese & Vincenzi 2012; Cortese et al. 2019)
- Contrasting findings: No association between maternal CRP levels and ADHD risk (Chudal et al. 2020)

Could we be looking at
a **broader "syndrome,"**
with ADHD as one expression?

“So, what can one do, when faced with this mess? I know not the answers, I really must confess. But let’s take a step back, notice the patterns, ask the right questions, and then make connections — **a system’s perspective is what is suggested**.”



“And what might you discover? **A cluster of syndromes that journey together**, so common, yet hidden, from all but a few, who often themselves are suffering too; a cluster with lax joints right at its core, but with it there often comes a whole lot more; a cluster so toxic, inflaming the brain, and draining the mind of the joy and the drive, that keeps us alive.”

Immune / atopic conditions

(including allergies, asthma & autoimmunity)

Cardiovascular problems
(including both hypertension-related problems & autonomic / orthostatic problems)

Neurological issues
(especially sleep problems, epilepsy & migraines; possibly neurodegenerative)

CLUSTERS OF PHYSICAL HEALTH PROBLEMS IN ADULT ADHD

Conditions linked to ADHD lifestyle factors
(alcohol & smoking - related, STIs, etc.)

Hypermobility

Medication-related complications

Explainable Somatic Comorbidity

Obesity

Diabetic complications

Alcohol and drug-related complications

Sleep problems

Diabetes

Sexually transmitted infections

High blood pressure

+

Problems linked to ***ADHD MEDICATION***[1,2]

(e.g., high blood pressure and other cardiovascular issues, seizures)

1. Faraone SV, et al. *Neurosci Biobehav Rev.* 2021;128:789–818; 2. Instanes JT, et al. *J Atten Disord.* 2018;22(3)203–228.

ADHD's More Puzzling Somatic Associations

ASTHMA

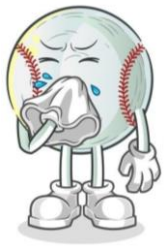
45 % more likely to have ADHD

(Cortese et al., 2018b)

ALLERGIC RHINITIS

about 50 % more likely to have ADHD

(van der Schans et al., 2017)



AUTOIMMUNE CONDITIONS

e.g., Ankylosing Spondylitis, Ulcerative Colitis, Thyroid disease (> 2 x prevalence in ADHD) *(Chen et al., 2017a)*

SLEEP DISORDERED BREATHING

(Sedky et al., 2014)

ABNORMALITIES OF THE EYE

- amblyopia, astigmatism, heterotropia *(Ho et al., 2020)*

MIGRAINE

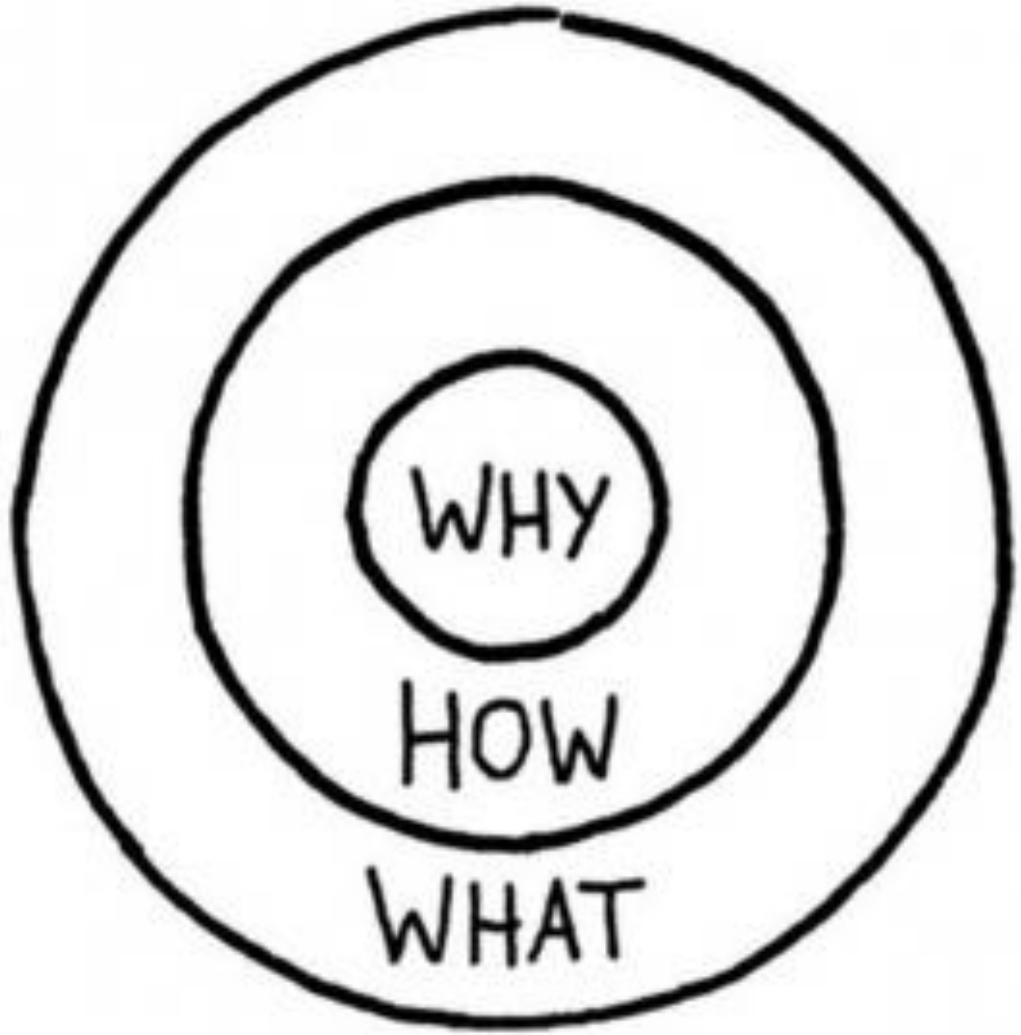
about 4 x more likely to have ADHD

(Arruda et al., 2020)

HYPERMOBILITY

5.6 x more likely to have ADHD

(Cederlöf M, et al., 2016)


WHY
HOW
WHAT

Immune / atopic conditions

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CLUSTERS OF PHYSICAL HEALTH PROBLEMS IN ADULT ADHD

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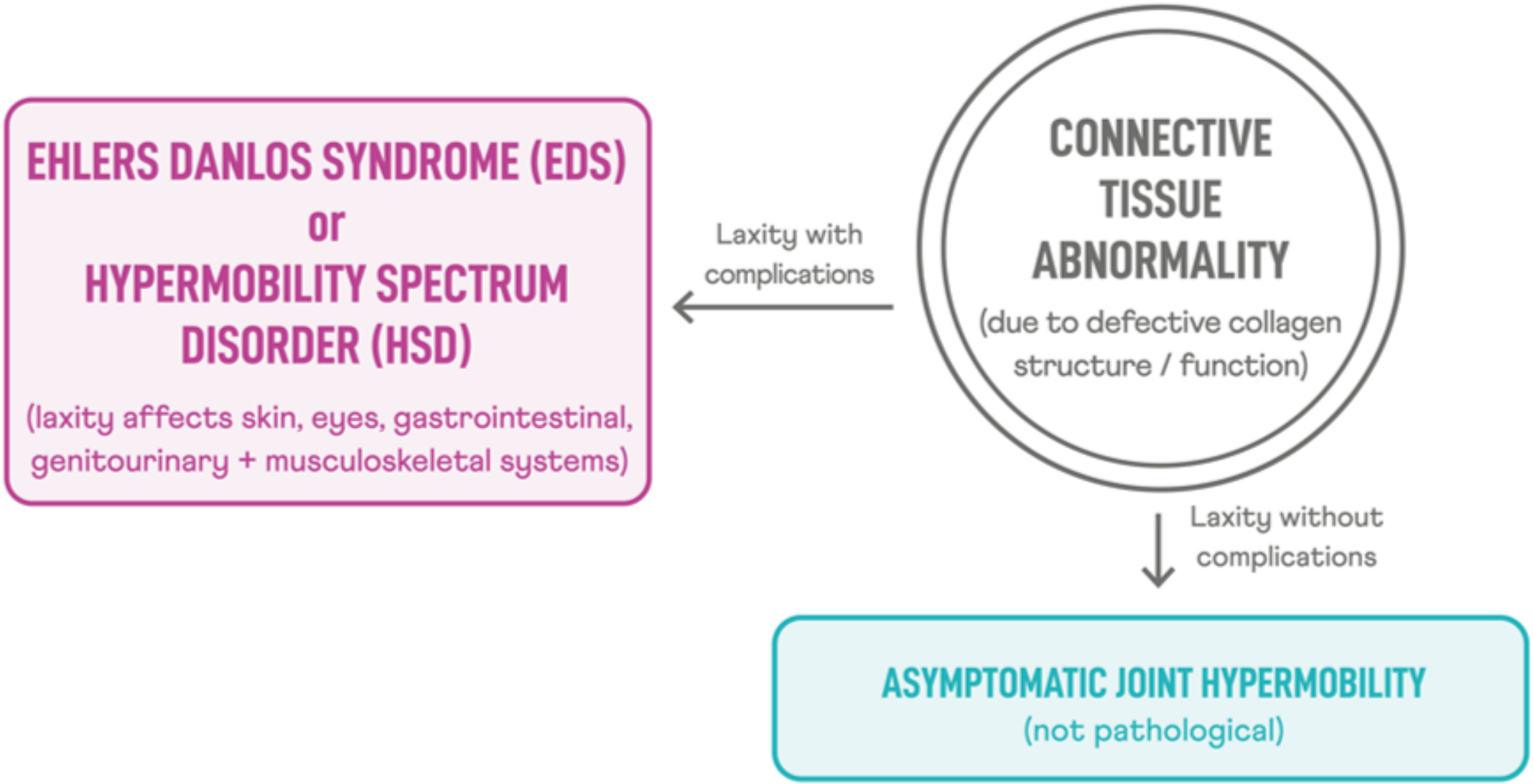
(alcohol & smoking - related, STIs, etc.)

Hypermobility

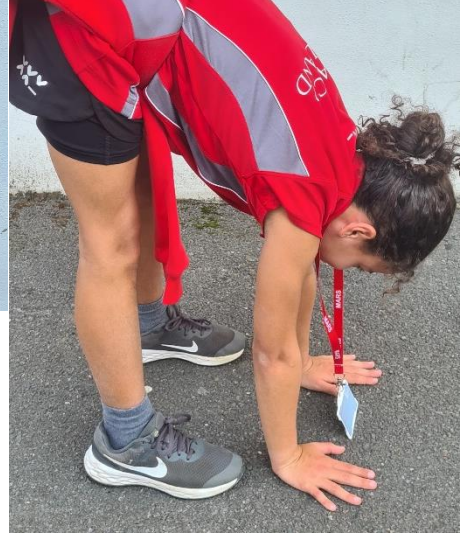
Medication-related complications

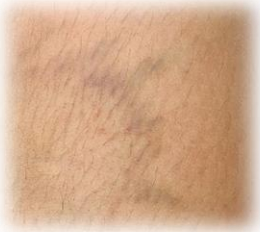
Lax joints, orthostatic symptoms & allergies

- 29-year-old woman diagnosed with ADHD
- also has features suggestive of autism
- long-standing hypermobility in various joints
- chronic lower back pain, recurrent ankle pain (and sprains), tendonitis, TMJ dysfunction, and soft skin which bruises easily
- dizziness, lightheadedness, palpitations on standing, recurrent fatigue
- intermittent nausea, acid reflux, and IBS symptoms (often triggered by certain foods)
- allergic to tree nuts and latex



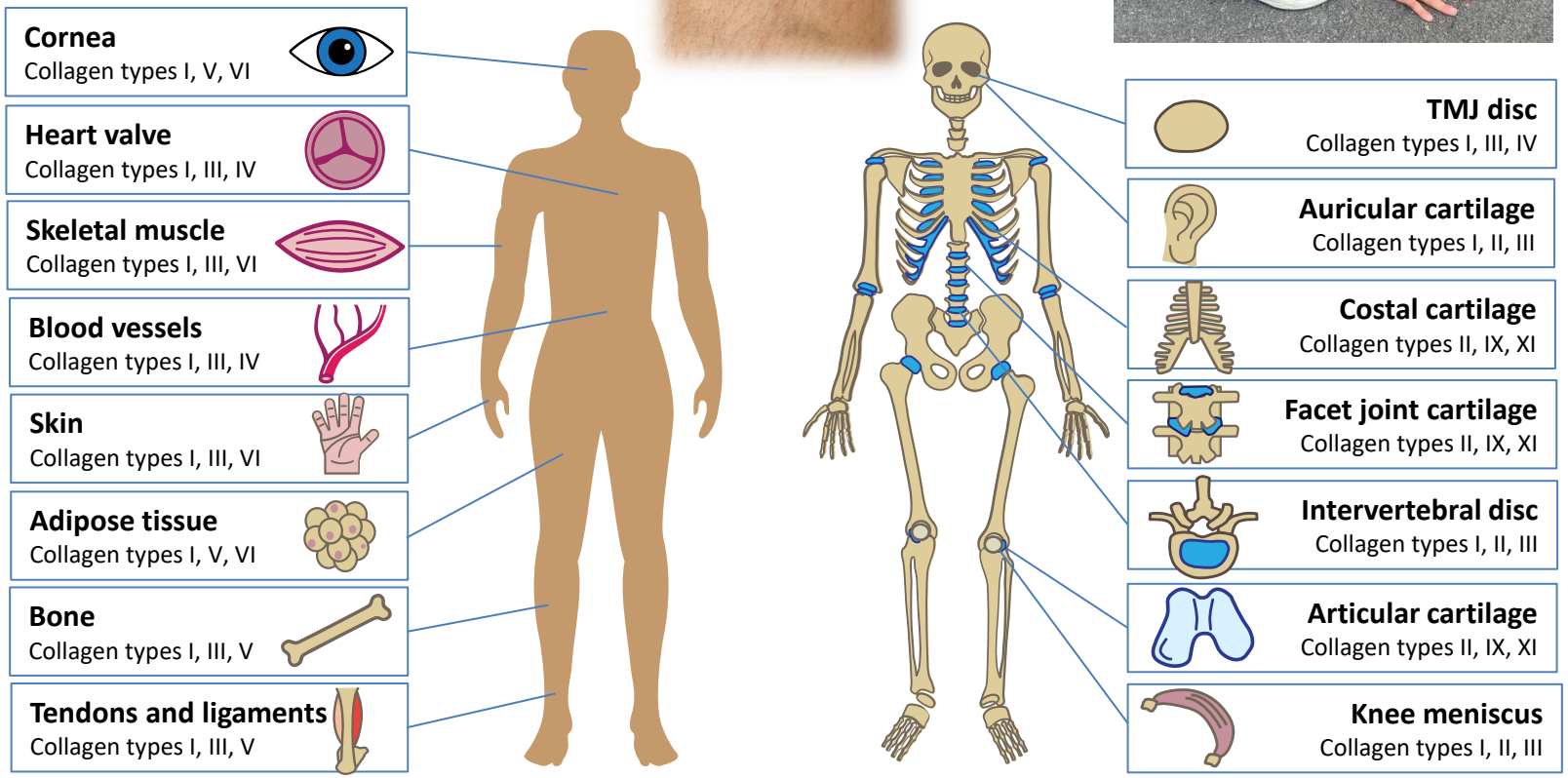
1. Castori M. *ISRN Dermatol*. 2012;2012:751768; 2. Speaker opinion and clinical experience.





- **Joint laxity** is common (present in ~10% – 30% of people)[1]
- Hypermobility + other symptoms
  = ***Ehlers-Danlos Syndrome (EDS)***
  or, if sub-threshold,
  = ***Hypermobility Spectrum Disorder (HSD)***[2]

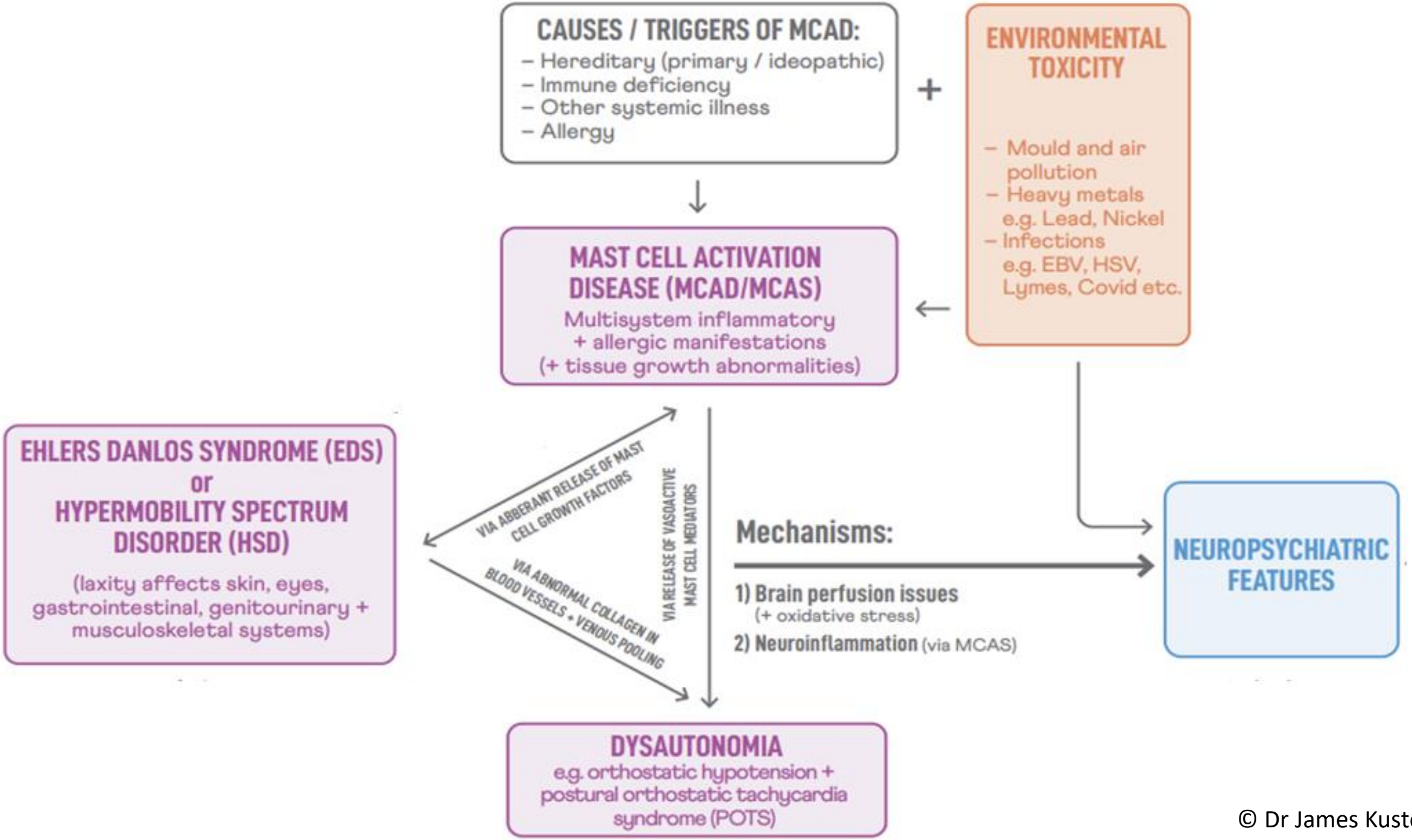
EDS
is a hereditary
connective tissue disorder
(defect in collagen production / function = laxity) with
multisystem effects[1,2]

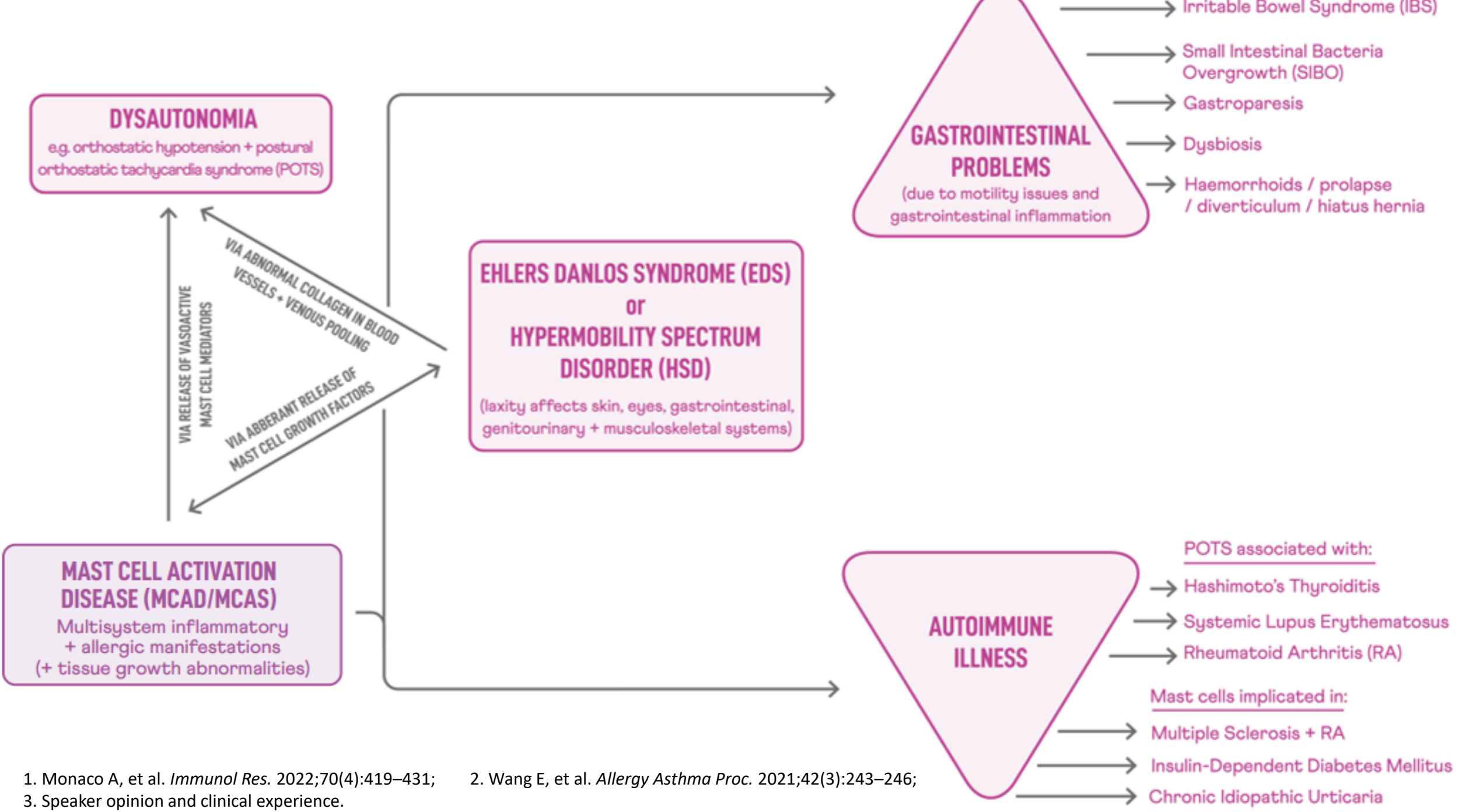


Adapted from Bielajew BJ, et al. 2020[3]

Connective tissues include ***tendons, ligaments, cartilage, intervertebral discs, skin, bones, eyes, viscera (organs),*** and, importantly, the ***blood vessels***[3]

1. Clinch J, et al. *Arthritis Rheum*. 2011;63(9):2819–2827; 2. Kindgren E, et al. *Neuropsychiatr Dis Treat*. 2021;17:379–388;
3. Bielajew BJ, et al. *Nat Rev Mater*. 2020; 5(10):730–747.





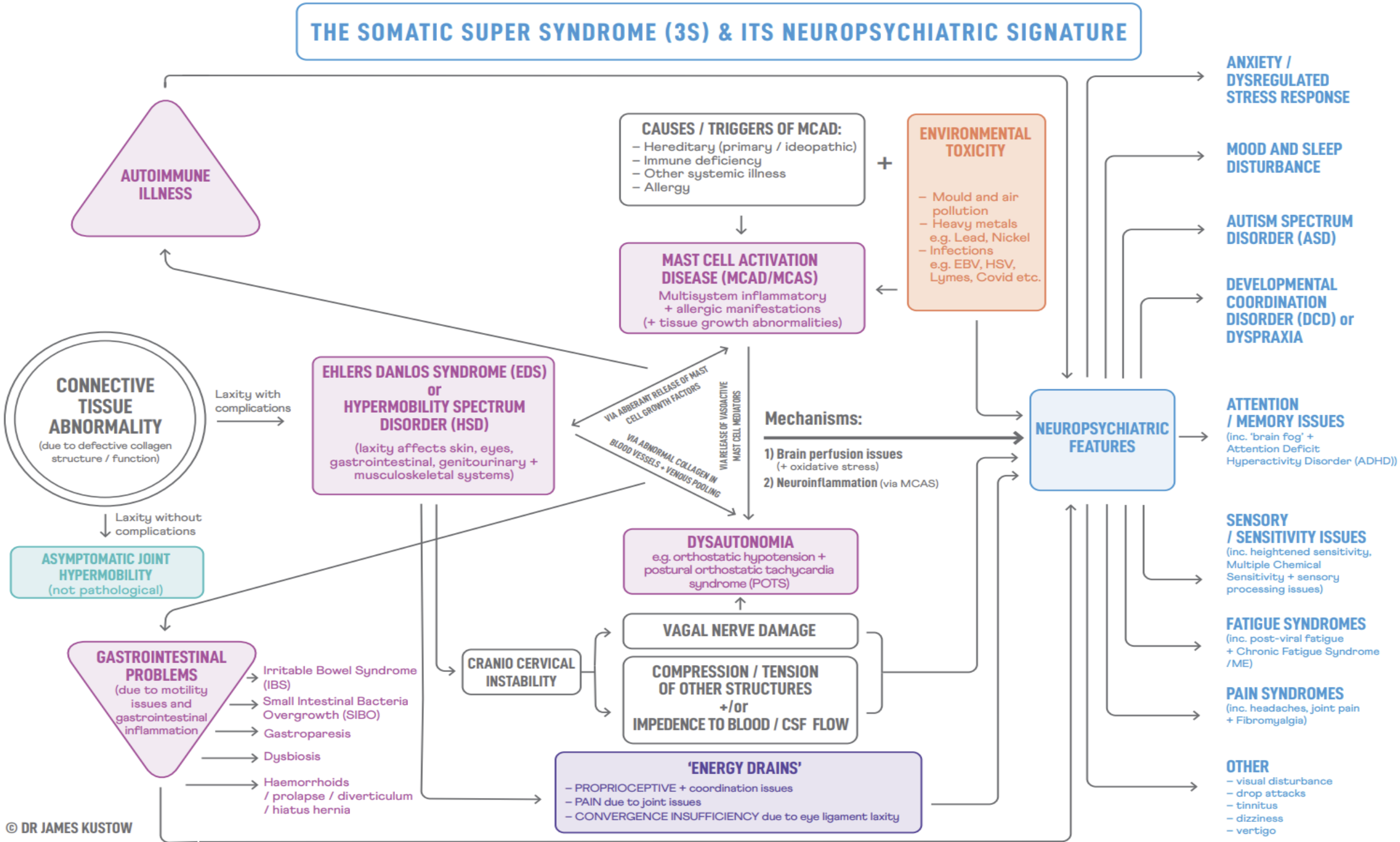
1. Monaco A, et al. *Immunol Res.* 2022;70(4):419–431; 2. Wang E, et al. *Allergy Asthma Proc.* 2021;42(3):243–246;
3. Speaker opinion and clinical experience.

Introducing the

Somatic Super-Syndrome

and Its Neuropsychiatric Signature

THE SOMATIC SUPER SYNDROME (3S) & ITS NEUROPSYCHIATRIC SIGNATURE



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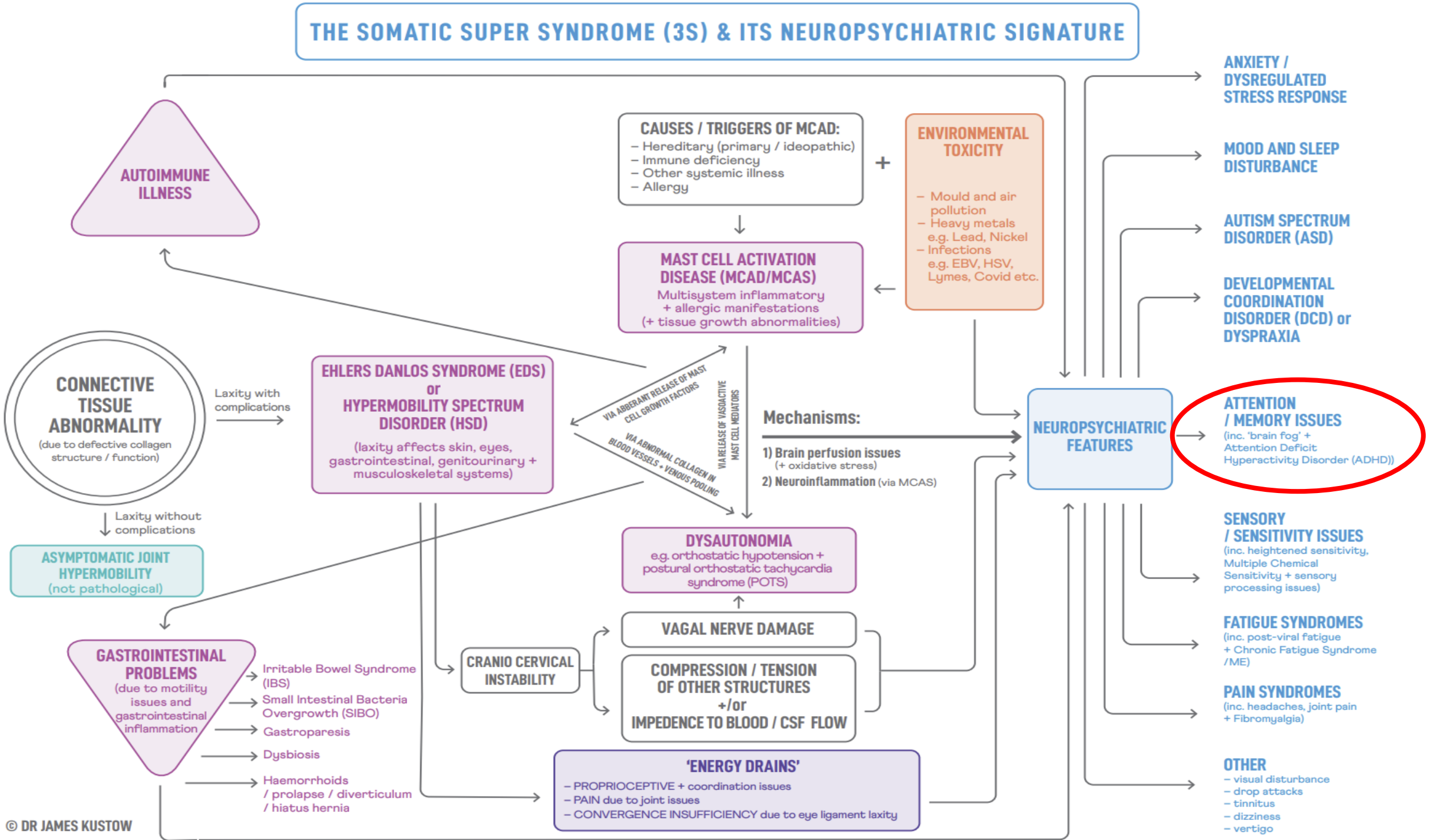

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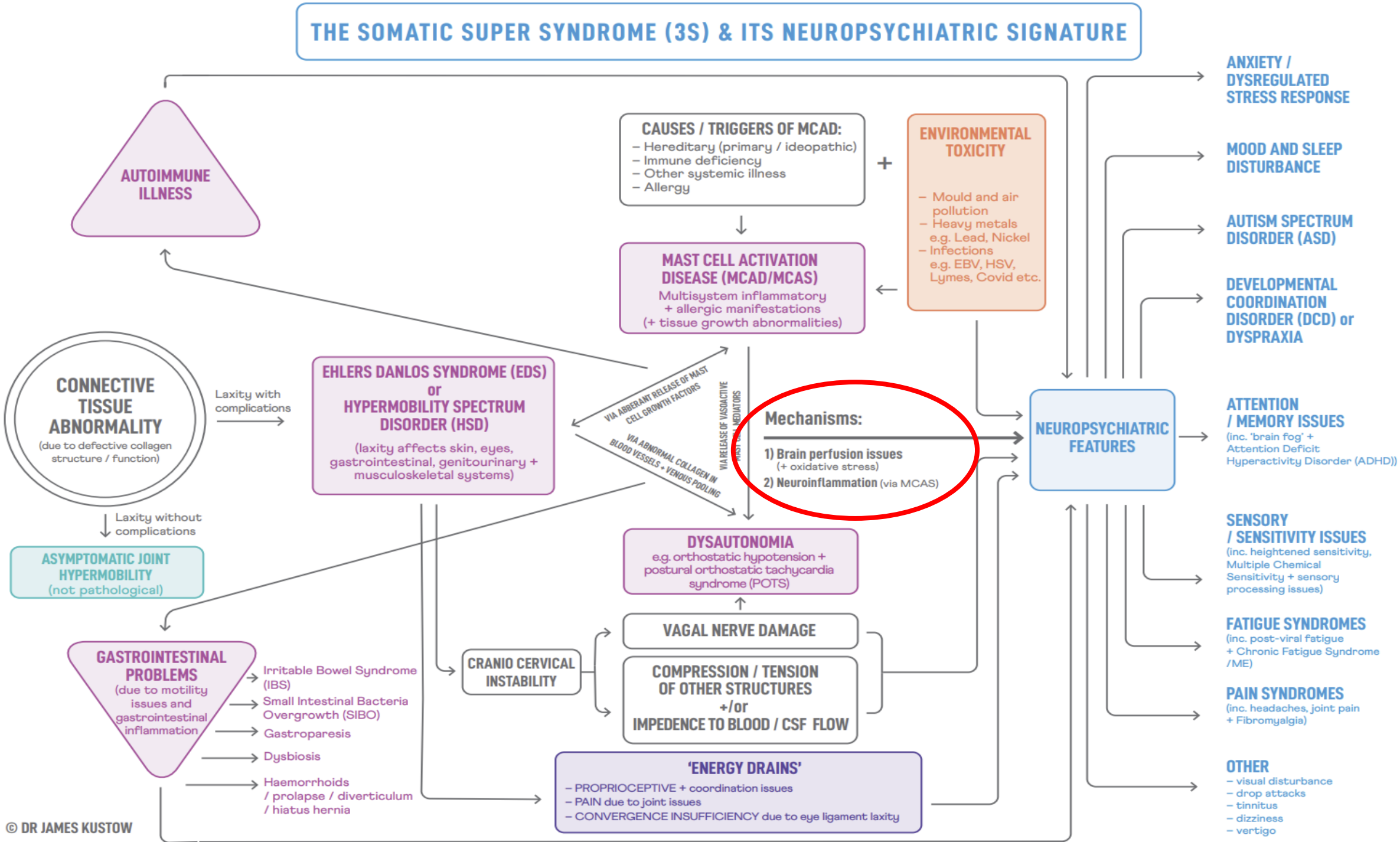
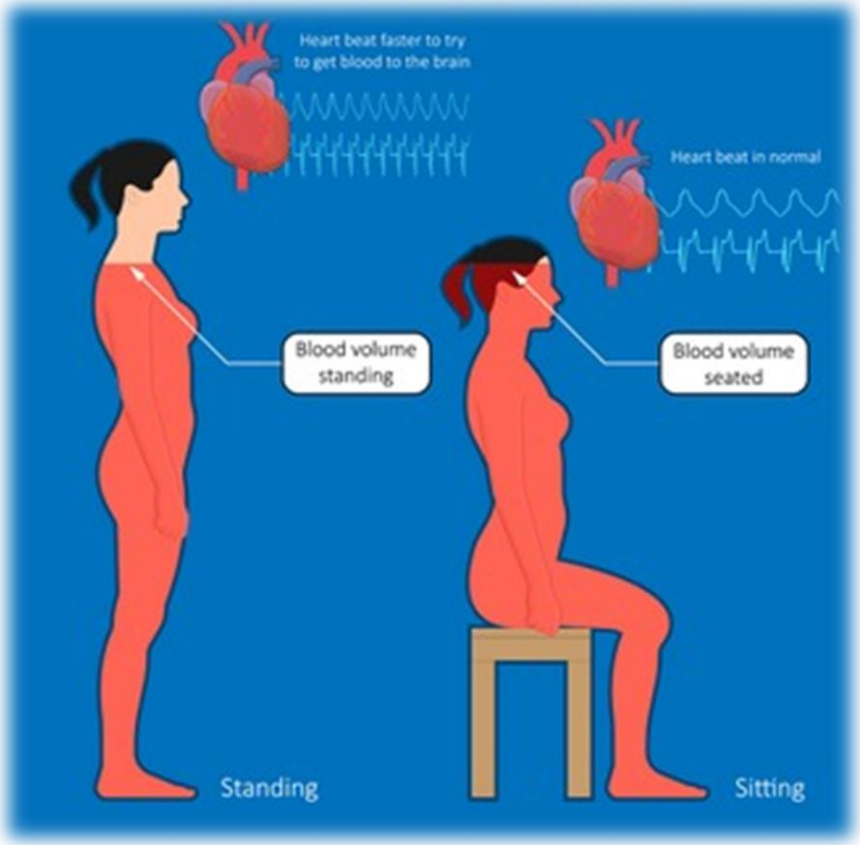
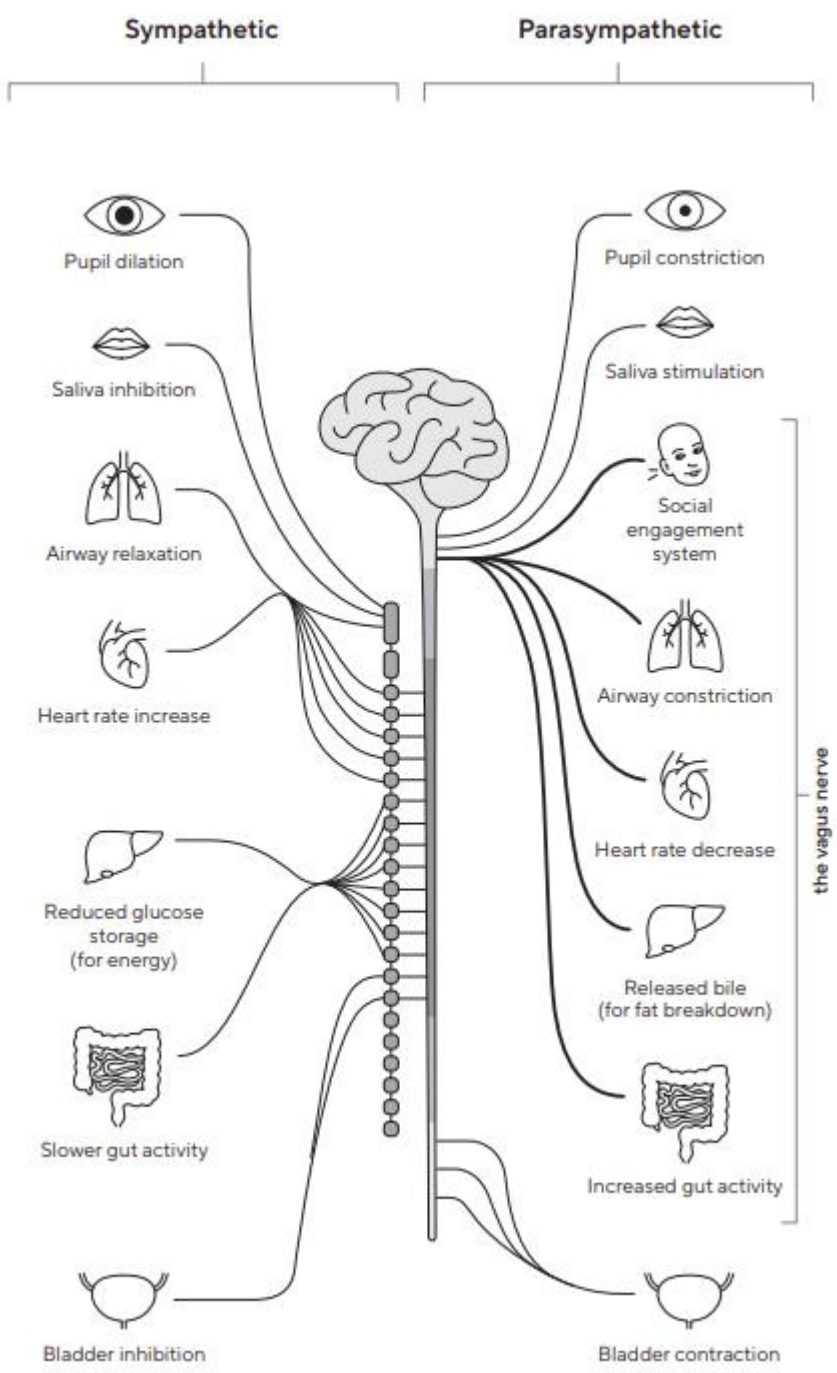


Possible *Mediators* of ADHD Symptoms

1. **Dysautonomia**

2. **Neuroinflammation**





The Autonomic Nervous System

(and the vagus nerve)

The ANS includes:

1. **Parasympathetic nervous system** (relaxation response)
2. **Sympathetic nervous system** (stress response)

Dysautonomia & ADHD

- Dysautonomia is often associated with **orthostatic intolerance (OI)**, the phenomenon of ***experiencing symptoms when standing upright*** (due to insufficient blood supply to the brain)

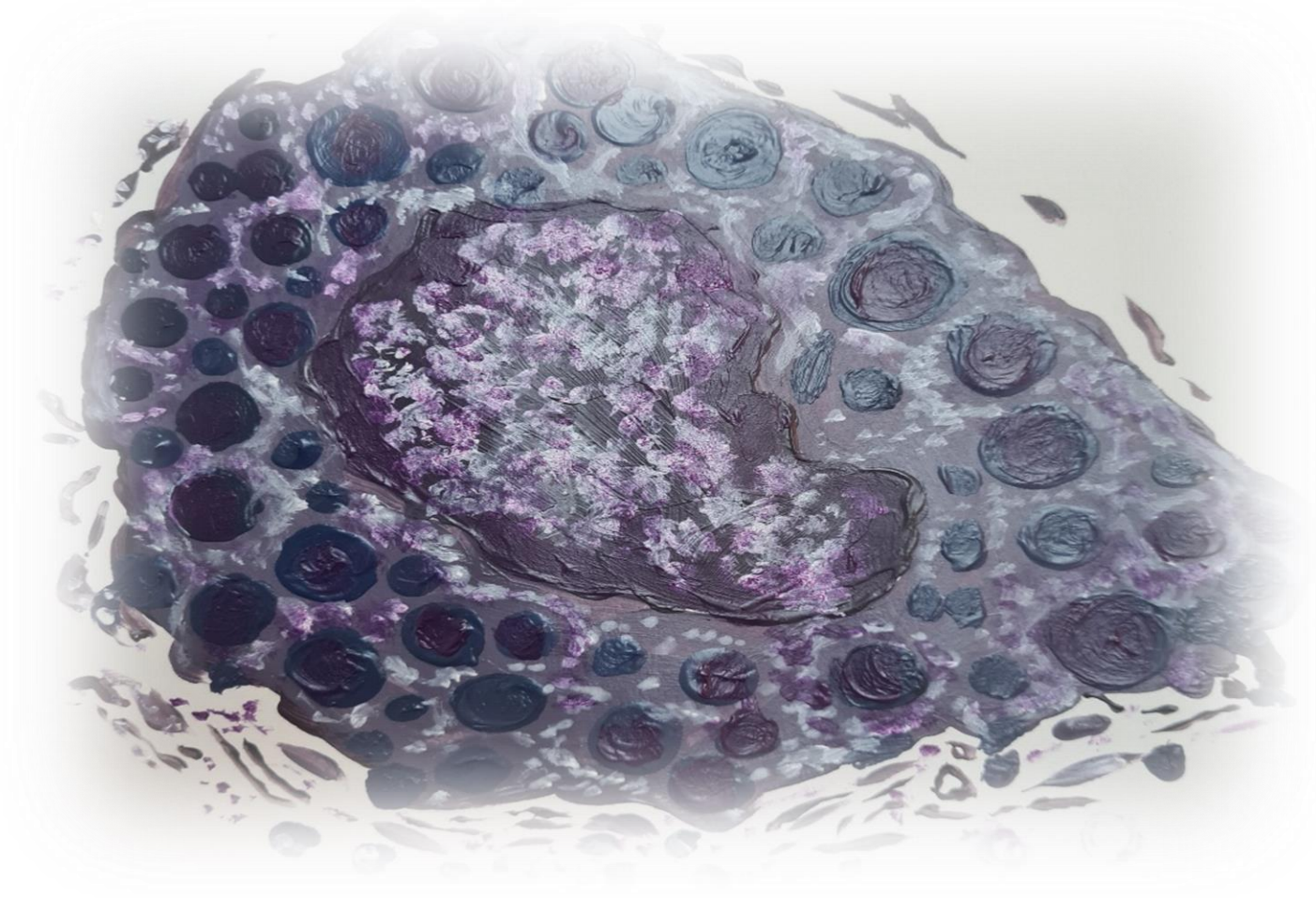
- It can also manifest as **Postural Orthostatic Tachycardia Syndrome (POTS)** & other conditions

Like ADHD, dysautonomia can start in childhood,
and **it can cause many of the symptoms we understand to be ADHD**

Possible *Mediators* of ADHD Symptoms

1. **Dysautonomia**

2. **Neuroinflammation**



Mast Cells – “First Responders”

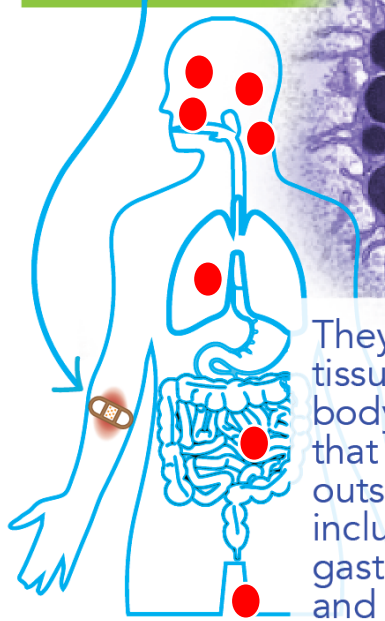
What is a MAST CELL?

Mast cells are a part of the **immune system**.

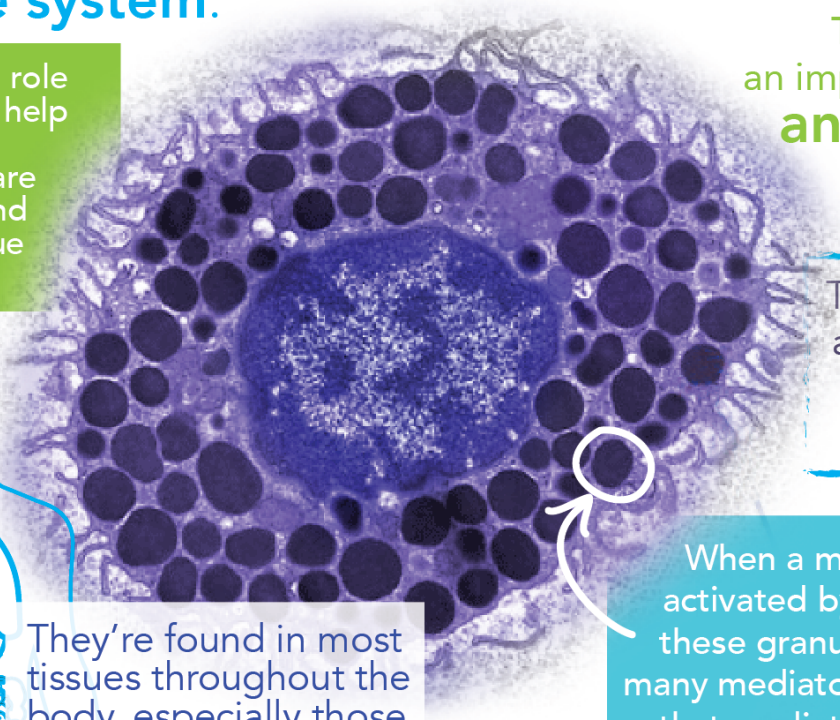
Mast cells are well-known for releasing histamine during allergic reactions, such as in pollen or insect sting allergies.

They play an important role in **anaphylaxis!**

Mast cells play a role in inflammation, help defend against pathogens and are involved in wound healing and tissue repair.



They're found in most tissues throughout the body, especially those that interact with the outside environment, including the lungs, gastrointestinal tract and skin.



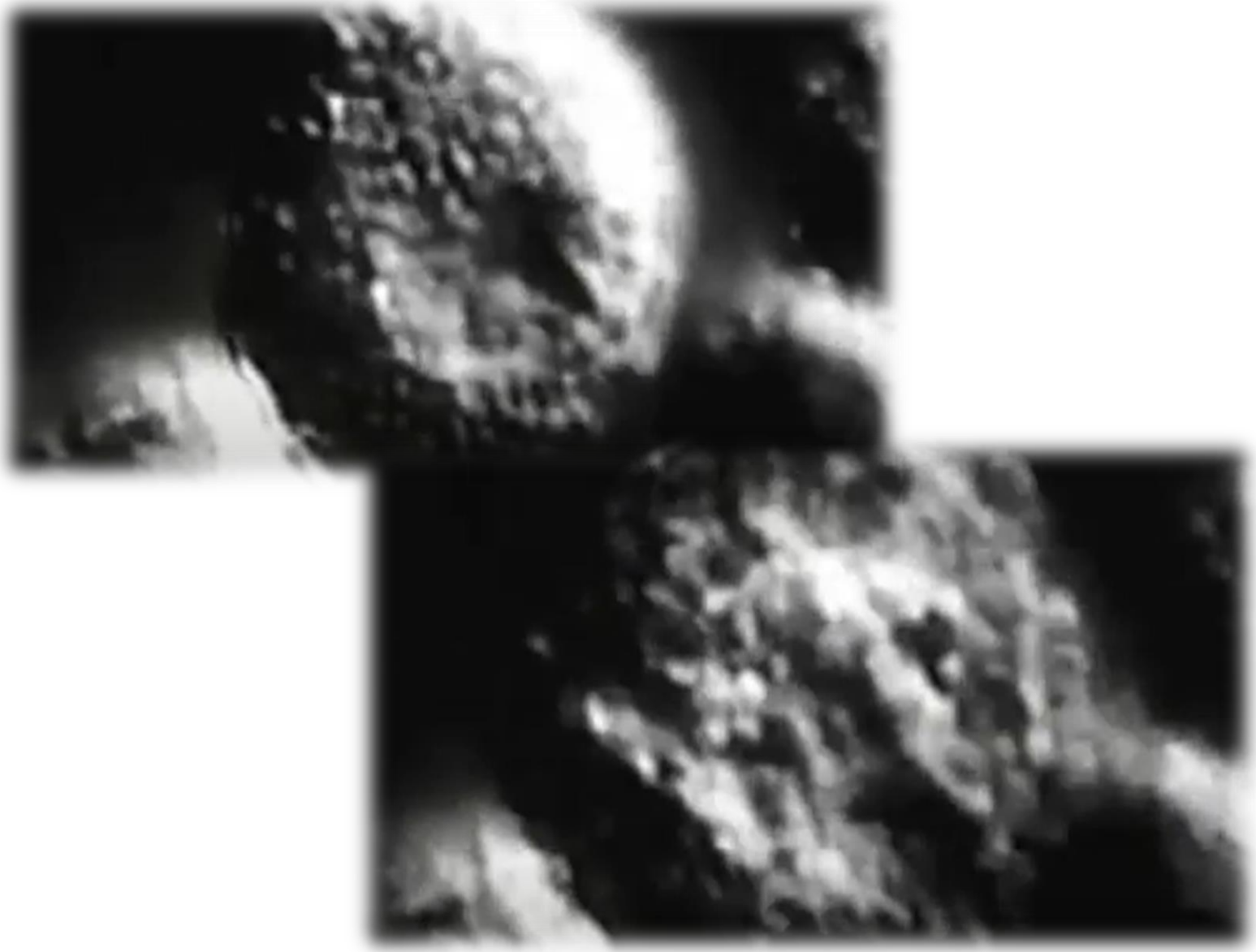
They can detect and respond to foreign substances.

When a mast cell is activated by a trigger, these granules release many mediators (chemicals that mediate reactions leading to symptoms).

histamine is a mediator

MAST CELL DISEASE happens when these cells aren't behaving normally.

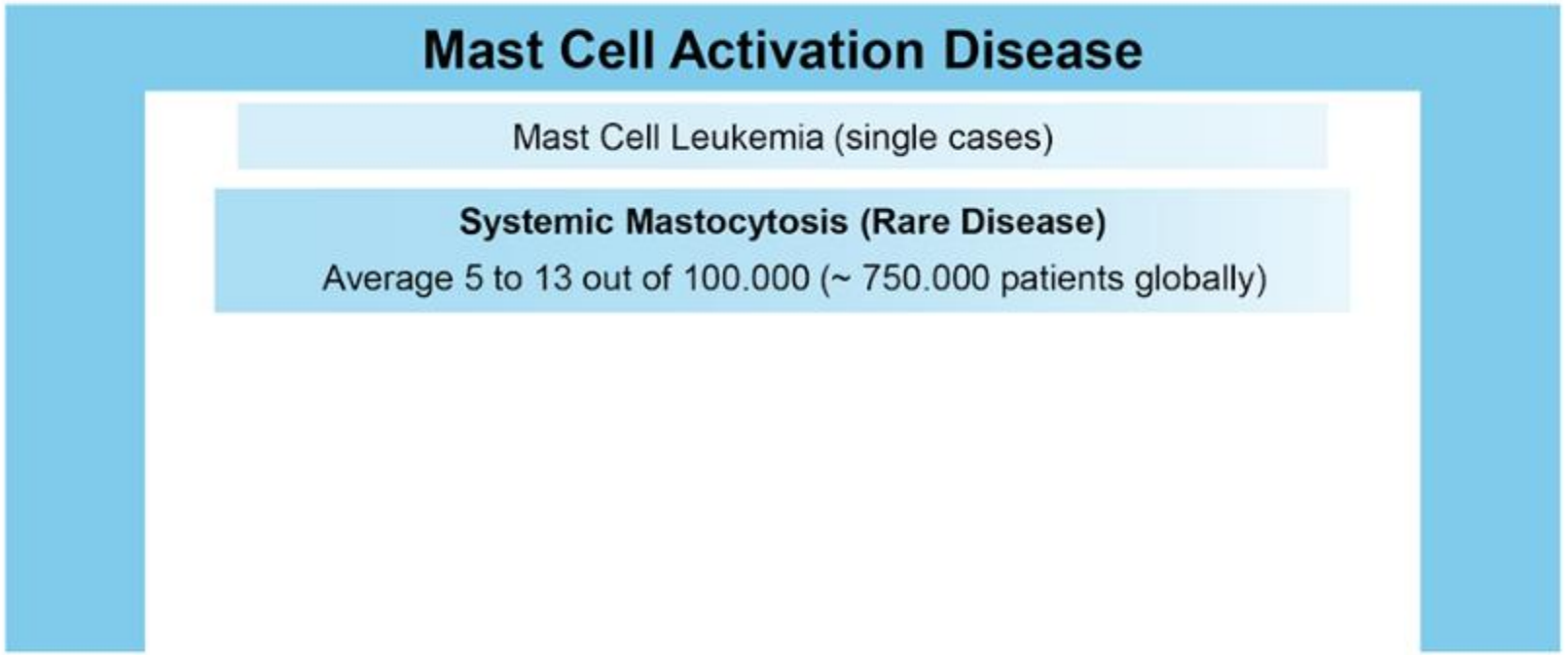
Resource adapted from the Mast Cell Disease Society



Real-Time Activation of a Mast Cell by Substance P

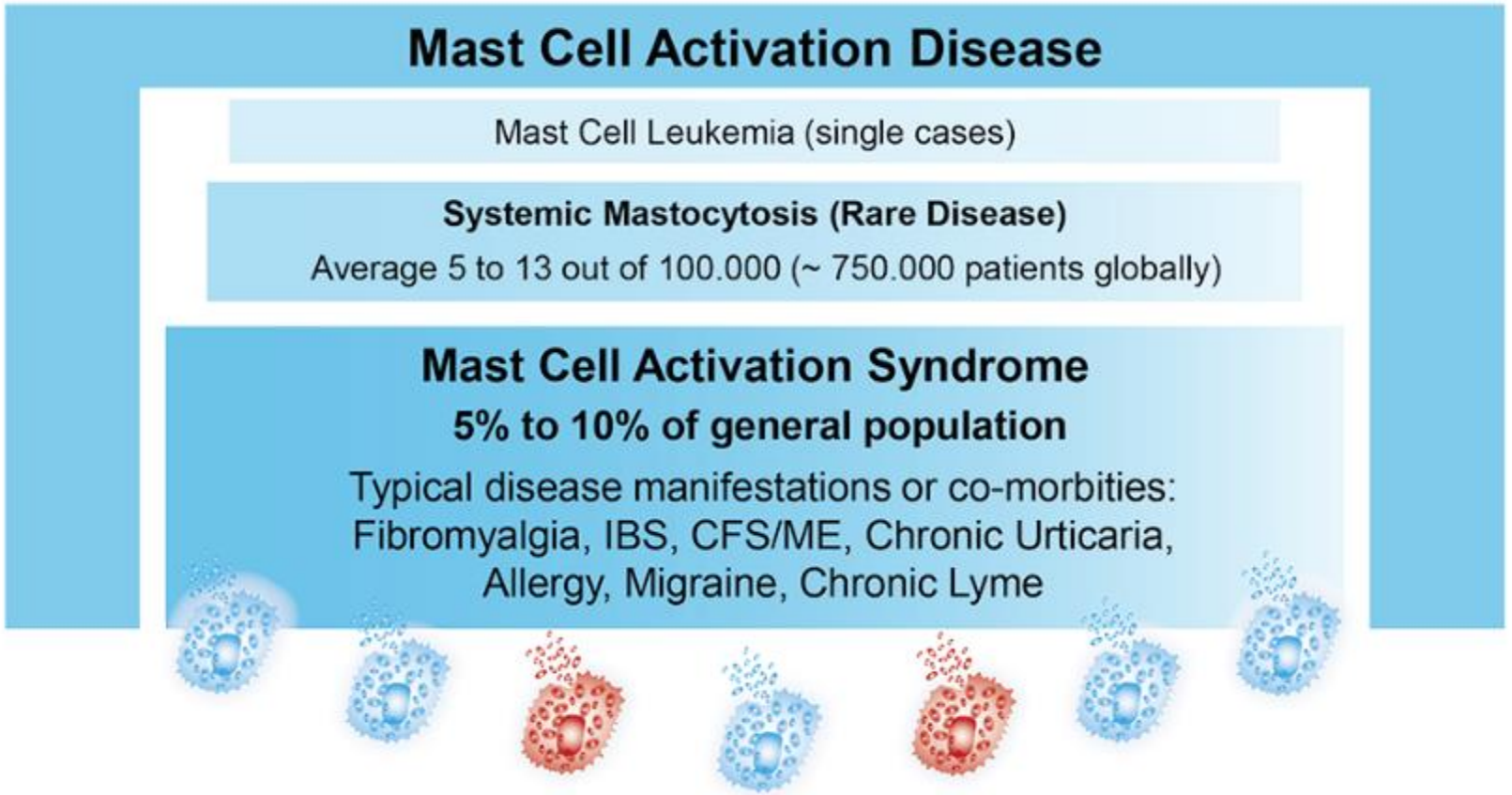
https://youtu.be/K8LCf_GbBE8

Theoharides, T. C., et al. (2015). Mast Cells, Mastocytosis, and Related Disorders. *The New England journal of medicine*



There are two main forms of Mast Cell Activation Disease:

(i) those **associated with abnormal mast cell proliferation (***e.g,. mast cell tumors, mast cell leukemia, systemic* ***mastocytosis****, cutaneous mastocytosis* – these disorders are **RARE**, but need consideration



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(i) those **associated with abnormal mast cell proliferation (***e.g., mast cell tumors, mast cell leukemia, systemic* ***mastocytosis****, and cutaneous mastocytosis* – these disorders are **RARE**, but need consideration

(ii) those that are **NOT associated with abnormal mast cell proliferation** (i.e., the abnormality just relates to excessive or inappropriate activation of mast cells), referred to as ***MAST CELL ACTIVATION SYNDROME***

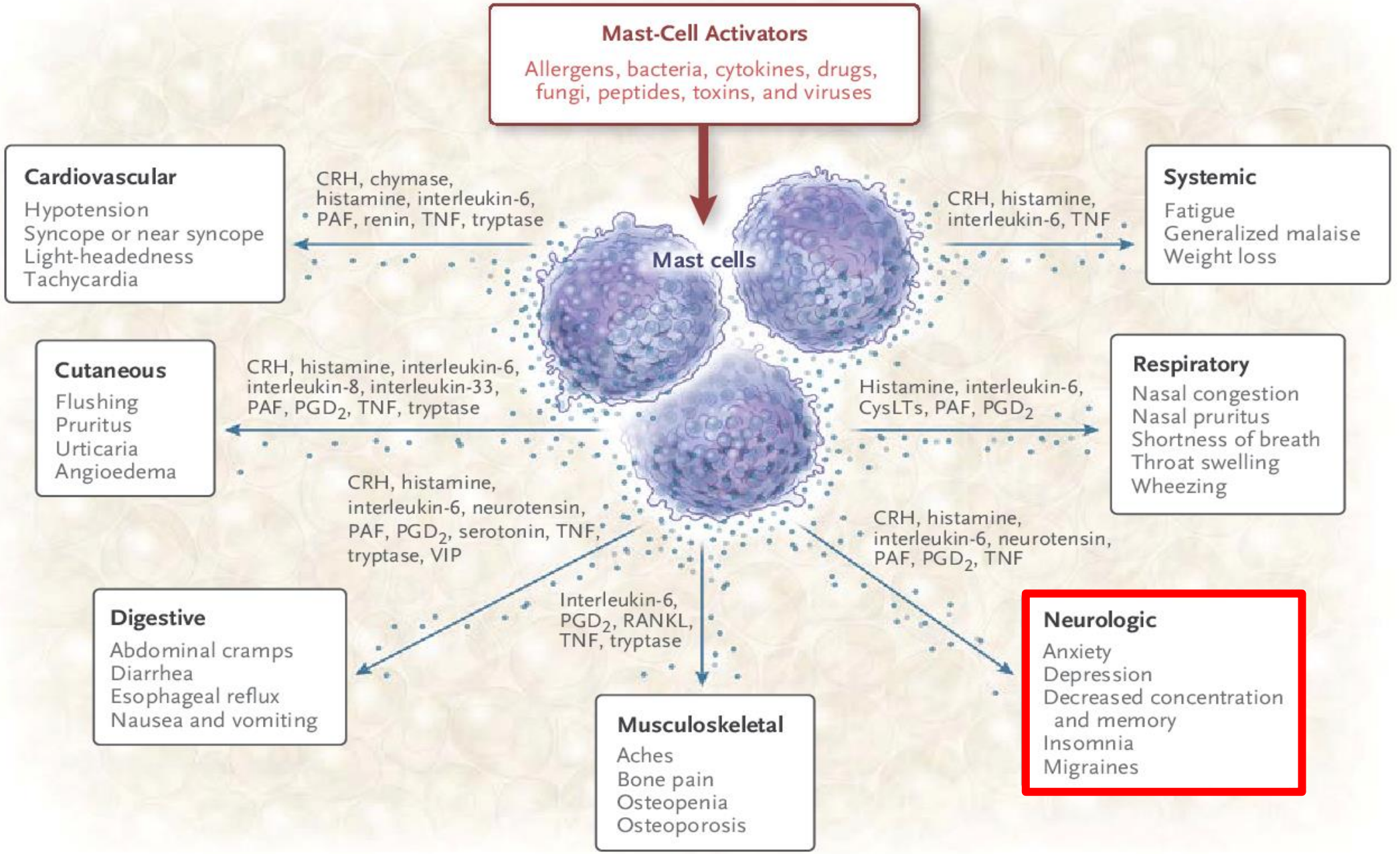


Figure 1. Clinically Relevant Mediators Released from Mast Cells and Putative Effects.

Theoharides, T. C., et al. (2015). Mast Cells, Mastocytosis, and Related Disorders. *The New England journal of medicine*

Mast Cell Activation Syndrome (MCAS) – An Overview

- A **recently defined**, still controversial, immune system-based disorder – can be **1er**, **2er** or **idiopathic.**
- In MCAS, **mast cells are inappropriately (and excessively) activated**, causing them to release **too many chemical mediators**, causing a **wide range of symptoms.**
- Mediators are typically inflammatory, causing multisystem **allergic-type symptoms.** (However, some are responsible for **growth and repair of tissue.**)
- MCAS emerges over time — characterized by **distinct phases ("flares") of symptoms** (often triggered)**,** which are **constitutional** (i.e., affecting whole system, like fatigue) or **multisystem.**
- Importantly, there are **PROMINENT NEUROPSYCHIATRIC SYMPTOMS** (note overlap with **ADHD**):

Fatigue | **Headache** | **Heightened Sensitivity** | **Anxiety** | **Sleep Disturbance** | **Concentration difficulties** | **Memory difficulties**

Mast Cell TRIGGERS (or 'Activators')

1. ***Infections*** *or* ***fever*** — including glandular fever (or EBV), Lyme's Disease and **COVID-19**

2. ***Physical stimuli*** — including pressure, friction, and in some cases, exercise

3. ***Stress*** *or* ***psychological trauma*** — mast cells have surface receptors for *Cortisol Releasing Hormone*

4. ***Allergens*** including Hymenoptera stings (and "pseudoallergy" where there is no antibody response but there may be severe symptoms); ***Drugs*** (including antibiotics, NSAIDs, neuromuscular blocking agents, radiocontrast media); ***Toxins*** (in household / self-care products or the environment); ***Foods / alcohol*** (often those that have a high histamine content / release histamine)

5. ***Changes to the environment*** — heat, cold, atmospheric pressure changes, mold, and EMR

6. ***Changes to the hormonal milieu*** — e.g., menstrual / menopausal hormone shifts

[Adapted from Cardet et al., 2013; Picard et al., 2013; Afrin (various)]

Neuropsychiatric Conditions with Established Associations with Mast Cell Dysfunction

ALZHEIMER'S DISEASE

- Mast cell activation accelerates the path to Alzheimer's disease
- CRH concentrations raised in affected brain areas

(Nelissen et al. 2013,

Shaik-Dasthagirisaheb et al. 2016)

MULTIPLE SCLEROSIS

- Mast cells are present in demyelinating lesions

(Ibrahim et al. 1996)

FIBROMYALGIA

- Higher levels of mast cell mediators (including CRH and substance P) and activated mast cells found in fibromyalgia

(Lucas et al. 2006)

AUTISM SPECTRUM DISORDER

- Associations established in 2016 study *(Theoharides et al.)*
- Higher levels of inflammatory mediators (e.g., TNF alpha, IL6 in brain tissue)

(Li et al. 2008)

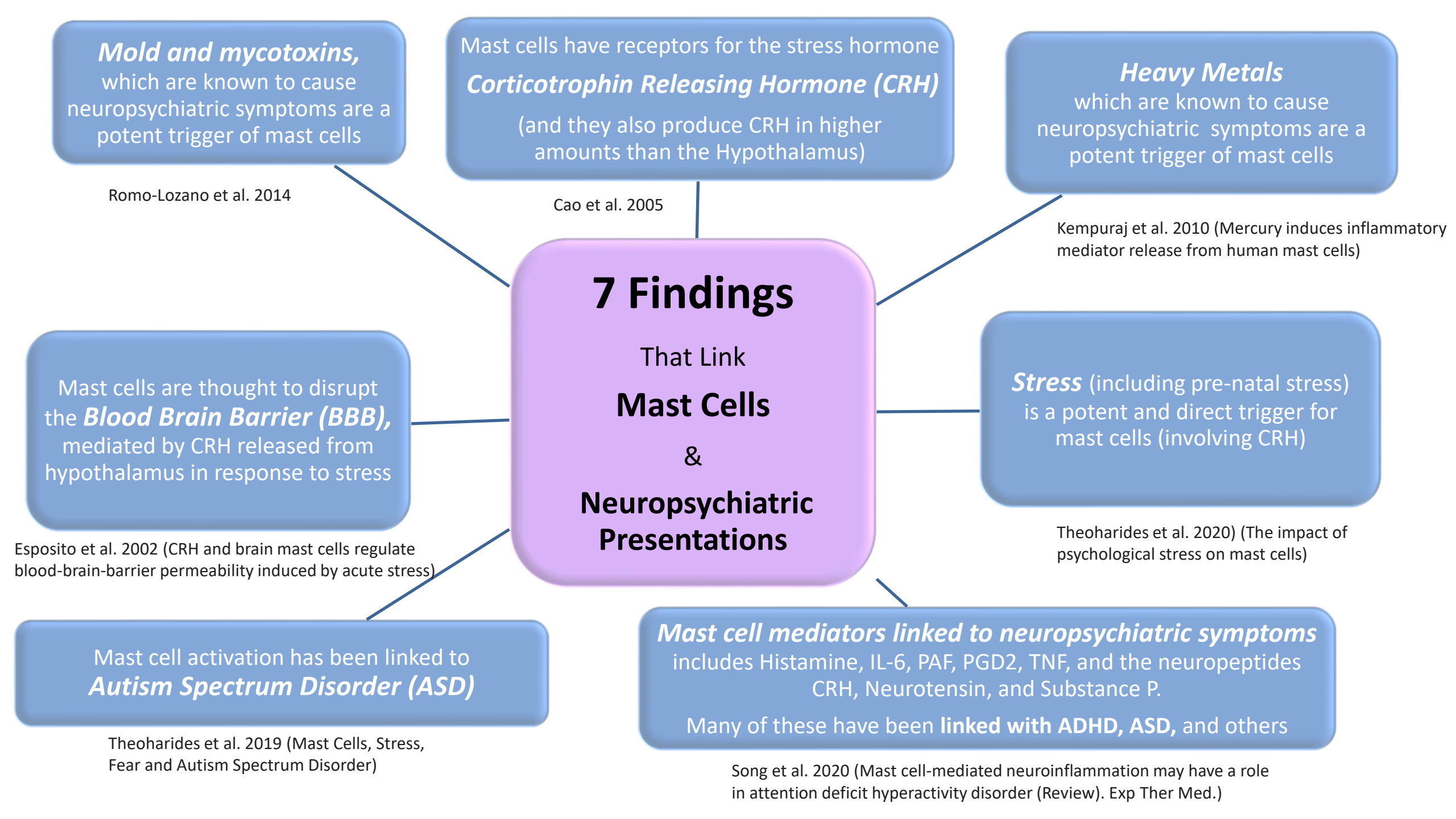
DEPRESSION

- Associated with Mastocytosis (40-70%) *(Georgin-Lavialle et al. 2016)*
- Mechanism via lower levels of tryptophan and serotonin *(Kawasaki et al. 2014)*
- Higher levels of kynurenic acid (its precursor known to promotes mast cell activation and associated with depression)

POST-TRAUMATIC STRESS DISORDER

- Higher concentrations of mast cells in tissues of those with PTSD
- Higher levels of CRH and other mediators
- More autoimmune and mast cell diseases

(Passos et al. 2015)


Mold and mycotoxins, which are known to cause neuropsychiatric symptoms are a potent trigger of mast cells
Romo-Lozano et al. 2014
Mast cells have receptors for the stress hormone ***Corticotrophin Releasing Hormone (CRH)*** (and they also produce CRH in higher amounts than the Hypothalamus)
Cao et al. 2005
Heavy Metals which are known to cause neuropsychiatric symptoms are a potent trigger of mast cells
Kempuraj et al. 2010 (Mercury induces inflammatory mediator release from human mast cells)
7 Findings
That Link
Mast Cells
&
Neuropsychiatric Presentations
Mast cells are thought to disrupt the ***Blood Brain Barrier (BBB),*** mediated by CRH released from hypothalamus in response to stress
Esposito et al. 2002 (CRH and brain mast cells regulate blood-brain-barrier permeability induced by acute stress)
Stress (including pre-natal stress) is a potent and direct trigger for mast cells (involving CRH)
Theoharides et al. 2020) (The impact of psychological stress on mast cells)
Mast cell activation has been linked to ***Autism Spectrum Disorder (ASD)***
Theoharides et al. 2019 (Mast Cells, Stress, Fear and Autism Spectrum Disorder)
Mast cell mediators linked to neuropsychiatric symptoms includes Histamine, IL-6, PAF, PGD2, TNF, and the neuropeptides CRH, Neurotensin, and Substance P.
Many of these have been **linked with ADHD, ASD,** and others
Song et al. 2020 (Mast cell-mediated neuroinflammation may have a role in attention deficit hyperactivity disorder (Review). Exp Ther Med.)

Linking Mast Cells to ADHD

- No studies to date have evaluated or demonstrated the role of mast cells in ADHD.
- A 2020 review (China), published in *Experimental and Therapeutic Medicine*, explores the hypothesis that ADHD is a neuroinflammatory disease involving mast cells (Song et al. 2020).

The role of mast cells in ADHD is supported by:

- ❑ Higher levels of mast cell-derived inflammatory mediators found in individuals with ADHD
- ❑ ADHD's physical health comorbidities
- ❑ The role of mast cells in chronic neuroinflammation, which could underpin ADHD symptoms
- ❑ The established associations between mast cells and other neuropsychiatric presentations
- ❑ The mast cell activating effects of chronic stress (via CRH), a hallmark feature of ADHD
- ❑ The mast cell's impact on BBB permeability, which could explain the chronic nature of ADHD

Toxicity & Inflammation

- Toxins are **highly inflammatory**

- Entry points:
  1. ***Respiratory system***
  2. ***Gastrointestinal system***
  3. ***Skin***

- Immune system recognizes as foreign
  - = **Inflammatory response**
  - = **Altered ANS functioning**
  - = **Barrier compromise**
  - = **Neurotoxicity**

Are those with ADHD like canaries in the coal mine?

32 Family, twin, and DNA studies show that genetic and environmental influences are partially shared between ADHD and many other psychiatric disorders (e.g. schizophrenia, depression, bipolar disorder, autism spectrum disorder, conduct disorder, eating disorders, and substance use disorders) and with somatic disorders (e.g. migraine and obesity) (Demontis et al., 2019) (Faraone and Larsson, 2018) (Ghirardi et al., 2018) (Lee et al., 2019a,b) (Lee et al., 2013) (Anttila et al., 2018; Tylee et al., 2018) (van Hulzen et al., 2017) (Vink and Schellekens, 2018) (Brikell et al., 2018) (Chen et al., 2019a) (Yao et al., 2019). However, there is also a unique genetic risk for ADHD. Evidence of shared genetic and environmental risks among disorders suggest that these disorders also share a pathophysiology in the biological pathways that dysregulate neurodevelopment and create brain variations leading to disorder onset.

33 Very large studies of families suggest that ADHD shares genetic or familial causes with autoimmune diseases (Li et al., 2019), hypospadias (Butwicka et al., 2015), and intellectual disability (Faraone and Larsson, 2018).

7.2. Environmental correlates of ADHD: exposure to toxicants

34 A pair of meta-analyses found small correlations between lead burden and inattention symptoms (27 studies, over 9300 youths) and hyperactivity-impulsivity symptoms (23 studies, over 7800 youths) (Goodlad et al., 2013). A more recent meta-analysis of 14 studies with over 17,000 children reported that higher blood lead levels were associated with quadrupled odds of ADHD (Nilsen and Tulve, 2020). A study of over 2500 youths from the National Health and Nutrition Examination Survey, a cross-sectional, nationally representative sample of the U.S. population, found that those with blood lead levels in the top third were 2.3 times more likely to have ADHD compared with those in the bottom third (Froehlich et al., 2009). A similar study, with over 4700 youths from the same national survey, found that those with blood lead levels in the highest fifth were four times more likely to have ADHD compared with those in the bottom fifth (Braun et al., 2006).

35 Three meta-analyses with over twenty studies covering more than three million persons have found prenatal exposure to maternal smoking associated with a greater than 50 % increase in incidence of ADHD (Huang et al., 2018a) (Dong et al., 2018; Nilsen and Tulve, 2020). Although this association has also been seen in large population studies (Joelsson et al., 2016; Obel et al., 2016; Skoglund et al., 2014), it disappears after adjusting for family history of ADHD, which indicates that the association between maternal smoking during pregnancy and ADHD is due to familial or genetic factors that increase the risk for both smoking and ADHD.

36 A meta-analysis of nine studies spanning three continents and over 100,000 participants found that childhood exposure to secondhand cigarette smoke was associated with a 60 % greater likelihood of ADHD. It was unclear to what extent the association was causal versus due to confounders (Huang et al., 2021).

37 In a meta-analysis of 15 double-blind, placebo-controlled trials with 219 participants, artificial food dyes were associated with a small increase in hyperactivity in children (Schab and Trinh, 2004). Another meta-analysis, covering 20 studies with a combined total of 794 individuals, found a very small increase in ADHD symptoms, but only when rated by parents, not by teachers or other observers (Nigg et al., 2012).

38 In a Taiwanese study of over 10,000 births, maternal use of acetaminophen during pregnancy was associated with a 33 % greater likelihood of ADHD in their children (Chen et al., 2019b). Another study, examining 113,000 offspring from the Norwegian Mother and Child Cohort Study and the Norwegian Patient Registry, including 2246 with ADHD, found a dose-response relationship between maternal prenatal use of acetaminophen and ADHD (Ystrom et al., 2017).

39 A nationwide study using the Danish national registers looked at 913,000 children born between 1997 and 2011. Prenatal exposure to the anti-epileptic drug valproate was associated with a 50 % greater risk of ADHD. No associations were found for other anti-epileptic drugs (Christensen et al., 2019).

40 In a Norwegian registry study, 297 children with ADHD and 553 controls were randomly sampled from an eligible population of over 24,000. Children of mothers in the highest quintile of phthalate metabolite levels were three times more likely to have had ADHD as children compared with those in the bottom quintile, after adjusting for confounders, such as maternal age at delivery, sex of the child, maternal education, marital status, and prenatal maternal smoking (Engel et al., 2018).

41 Organophosphate pesticides are potent neurotoxins. In a sample of 1139 children from the U.S. population, a tenfold increase in the organophosphate metabolite dimethyl alkylphosphate (DMAP) was associated with 55 % increase in the probability of having ADHD. Children with detectable levels of the most-commonly detected DMAP metabolite were twice as likely to have ADHD compared with those with undetectable levels (Bouchard et al., 2010).

42 A meta-analysis found no significant effect of two classes of air pollutants – particulate matter (six studies, over 51,000 persons) and nitrogen oxides (five studies, over 51,000 persons) (Zhang et al., 2020b). A Taiwan-wide longitudinal cohort study geo-linking over 16,000 mother-infant pairs to levels of air pollutants found no association between small particulate matter levels, sulphur dioxide levels, or nitrogen dioxide levels during gestation and ADHD diagnoses in the first eight years of their offsprings' lives. It did find 25 % greater odds for having ADHD with exposures to nitric oxide, a common traffic pollutant (Shih et al., 2020).

43 A nationwide cohort study used the South Korean national health insurance registry to identify all 7200 hospital admissions of adolescents with a primary diagnosis of ADHD from 2013 to 2015, and daily readings of three air pollutants from 318 monitoring stations distributed across the country over the same period. It found that spikes in nitrogen dioxide, sulphur dioxide, and particulate matter were associated, respectively, with 47 %, 27 %, and 12 % increases in ADHD related hospital admissions in succeeding days. There were no significant differences between male and female adolescents, or between older and younger adolescents (Park et al., 2020).

44 A meta-analysis of nine European population studies encompassing 4826 mother-child pairs examined the relationship between exposure to Perfluoroalkyl Substances (PFAS) via breast milk in infancy and development of ADHD. No associations were found with ADHD in offspring (Forns et al., 2020).

45 A meta-analysis of seven studies encompassing a total of over 25,000 participants from six countries on three continents found no evidence of an association between sugar consumption and ADHD in youth (Farsad-Naeimi et al., 2020)

7.3. Environmental correlates of ADHD: nutrient deficiencies

46 A pair of meta-analyses found no difference in serum iron levels in youths with ADHD (six studies, 617 participants) but small-to-moderate reductions in serum ferritin, a protein that stores iron (ten studies, over 2100 participants) (Wang et al., 2017). Another pair of meta-analyses likewise found no difference in serum iron levels (six studies, over 1700 participants) but small-to-moderate reductions in serum ferritin (12 studies, over 6000 participants) (Tseng et al., 2018).

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The World Federation of ADHD International Consensus Statement: 208 Evidence-based conclusions about the disorder

Associations found with ADHD:

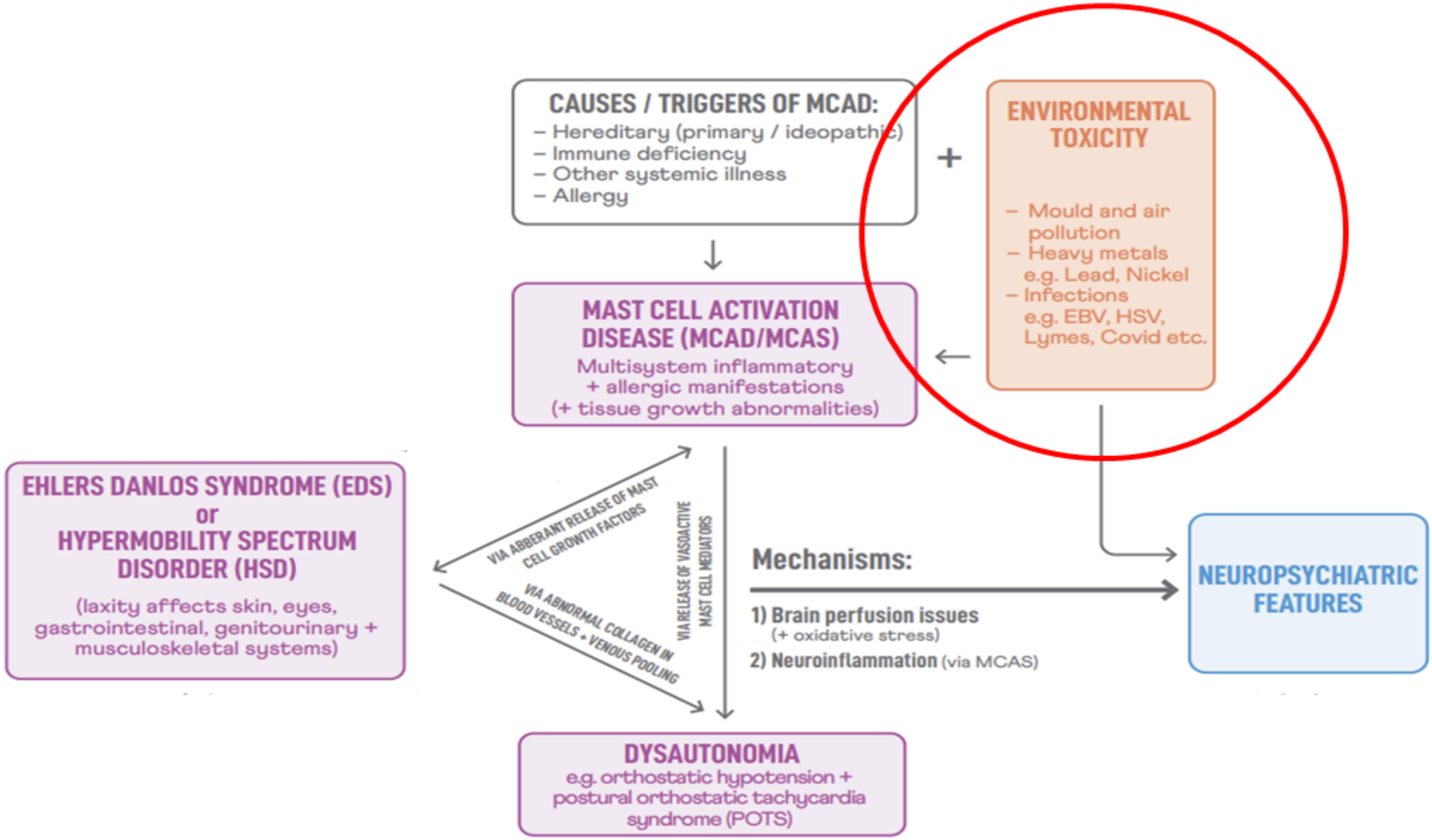
- ***Lead***
- ***Maternal smoking*** *and childhood* ***exposure to second-hand smoke***
- ***Artificial food dyes***
- *Maternal pre-natal* ***paracetamol*** *and* ***valproate*** *use*
- *DMAP* ***organophosphate metabolite***
- ***Air pollution*** *(particulate matter, NO, NO2 and SO2)*
- ***PFAS*** *via breast milk*

Indoor air toxicity

- **Air fresheners and other household / personal care products**
- **Furniture and furnishings** (*e.g., curtains, sofas, mattresses, and carpets)*
- **Building and decorating products** (*e.g., adhesives, fillers, paint, and varnishes*
- **Cigarette smoke**
- **Mold**

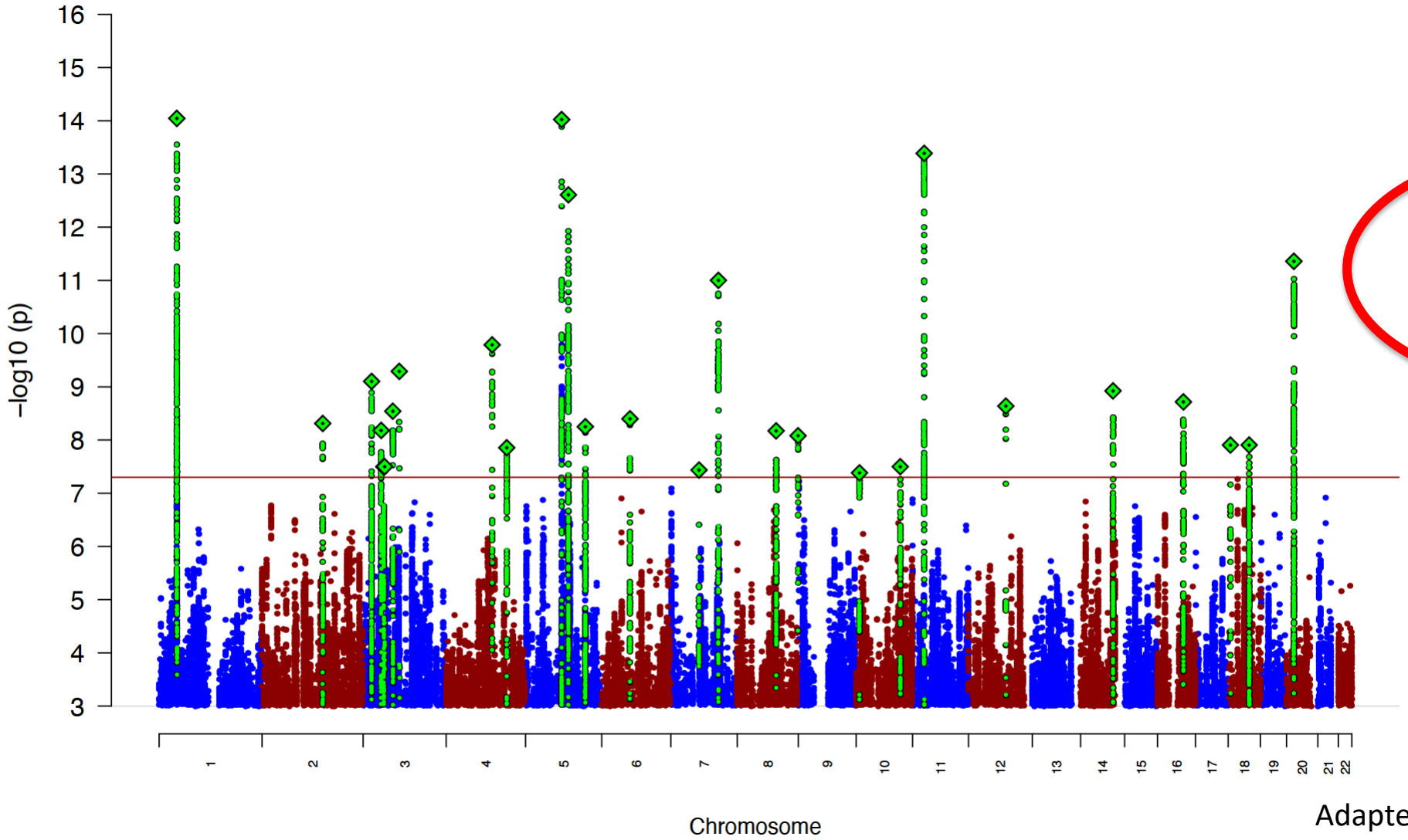
Mold (and mycotoxins)

- Under-recognized and serious
- Causes respiratory, musculoskeletal, and **neuropsychiatric issues (e.g., anxiety, brain fog, and irritability)**
- Mold growth promoted by:
  - *water leaks / ingress and damp environments and climates*
  - *rooms without airflow (and access to fresh air) and air conditioning units*
- Mycotoxins (released by the mold) exert powerful immune effects


CAUSES / TRIGGERS OF MCAD:
– Hereditary (primary / ideopathic)
– Immune deficiency
– Other systemic illness
– Allergy
+
ENVIRONMENTAL TOXICITY
– Mould and air pollution
– Heavy metals e.g. Lead, Nickel
– Infections e.g. EBV, HSV, Lymes, Covid etc.
MAST CELL ACTIVATION DISEASE (MCAD/MCAS)
Multisystem inflammatory + allergic manifestations (+ tissue growth abnormalities)
EHLERS DANLOS SYNDROME (EDS) or HYPERMOBILITY SPECTRUM DISORDER (HSD)
(laxity affects skin, eyes, gastrointestinal, genitourinary + musculoskeletal systems)
VIA ABBERANT RELEASE OF MAST CELL GROWTH FACTORS
VIA ABNORMAL COLLAGEN IN BLOOD VESSELS + VENOUS POOLING
VIA RELEASE OF VASOACTIVE MAST CELL MEDIATORS
Mechanisms:
1) Brain perfusion issues (+ oxidative stress)
2) Neuroinflammation (via MCAS)
NEUROPSYCHIATRIC FEATURES
DYSAUTONOMIA
e.g. orthostatic hypotension + postural orthostatic tachycardia syndrome (POTS)

ADHD GWAS Meta-Analysis (Manhattan plot)

(38,899 cases, 186,843 controls)



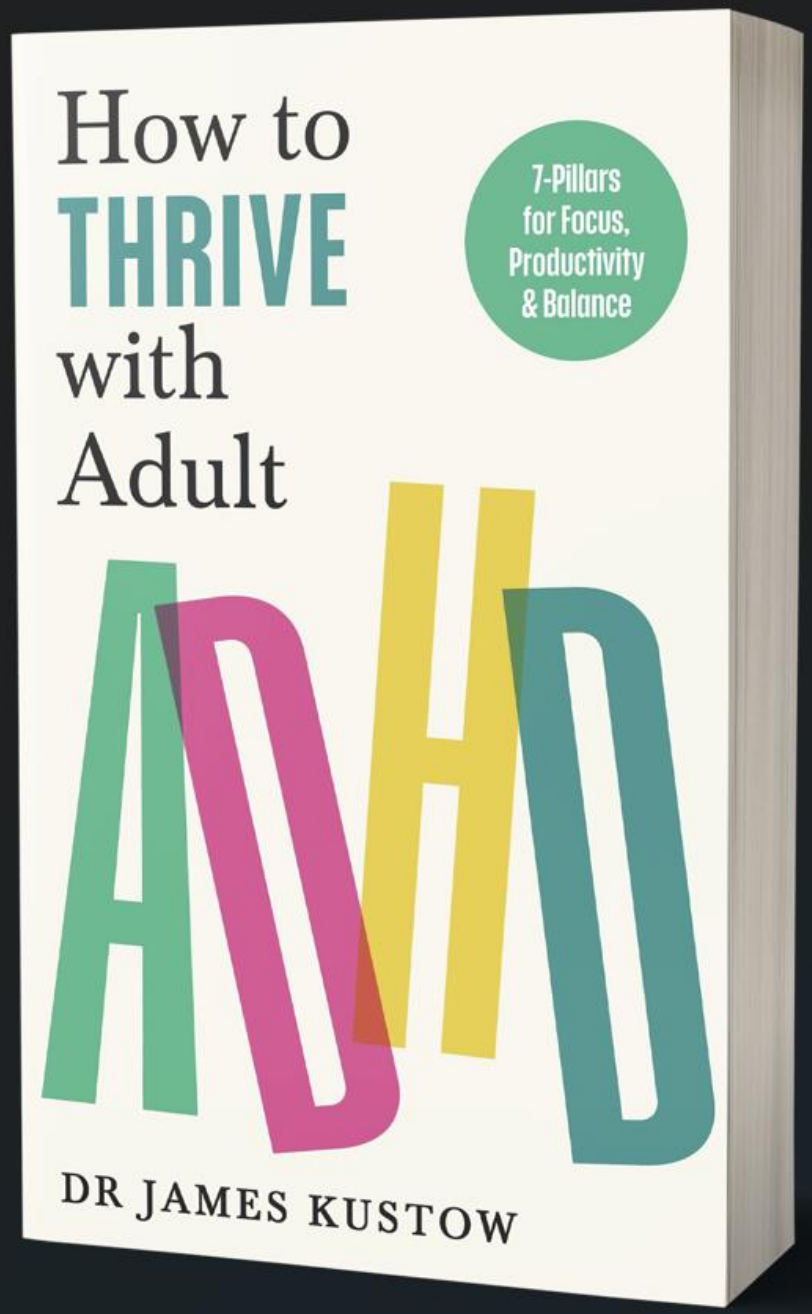
27 independent loci

Adapted from Demontis et al. 2022

3 Key Genes and Their *Various* Functions

[Adapted from Demontis et al., 2022]

Gene	Brain Functions	Immune Functions	Connective Tissue Functions	Strength of ADHD Association
MEF2C	Synaptic plasticity, memory, cognition, and neuronal survival	Regulates T-regulatory cells, mast cell differentiation, and immune suppression	Affects muscle differentiation, joint laxity, and muscle hypotonia	Highly significant (one of the strongest hits in ADHD GWAS)
FOXP1	Neural circuit formation, cognitive flexibility, social behaviors	Essential for B-cell development, modulates immune homeostasis	Involved in extracellular matrix remodelling, affecting connective tissue stability	Strong association with ADHD and neurodevelopmental disorders
SLC9A9	Regulates synaptic vesicle recycling, neurotransmitter transport, and executive functions	Controls intracellular pH regulation in immune cells, affecting mast cell response	Implicated in extracellular matrix maintenance and hypermobility syndromes	Strong association with ADHD, especially in executive function regulation



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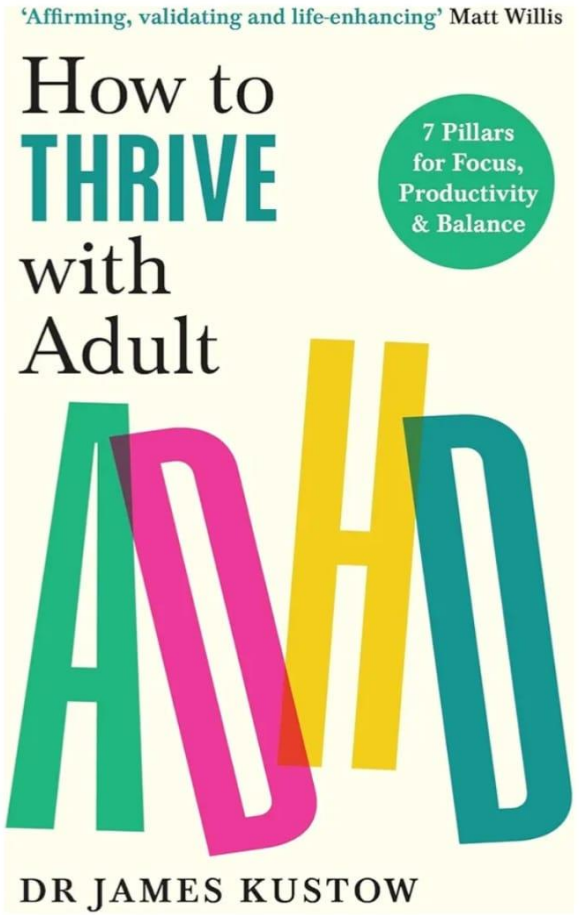
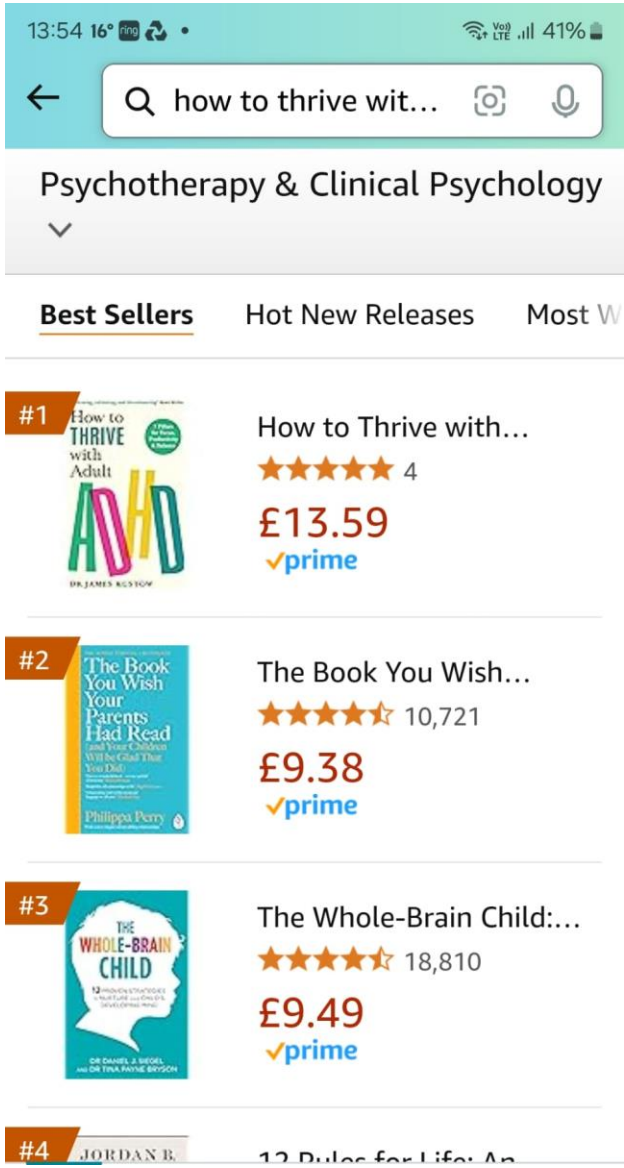
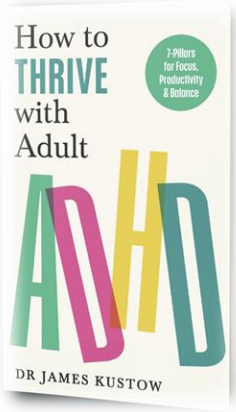




Two Onward Pathways @ The Grove



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- With Dr. James Kustow and Robert Rees
- Unpacking ADHD, establishing your ADHD signature, and building a plan
- Welcoming anyone who has or suspects they have adult ADHD (practitioners welcome)

Next intake: Friday 27th June 2025 (7th March FULL)

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- Exploring ADHD from a multisystem perspective, affecting mind, brain, and body
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Q&A

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- **Free Download:** Lifestyle Changes for Adults with ADHD
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- **Read:** Chronic Fatigue Twice as Likely Among Children with ADHD
- **Read:** Prenatal and Early Life Risk Factors of ADHD

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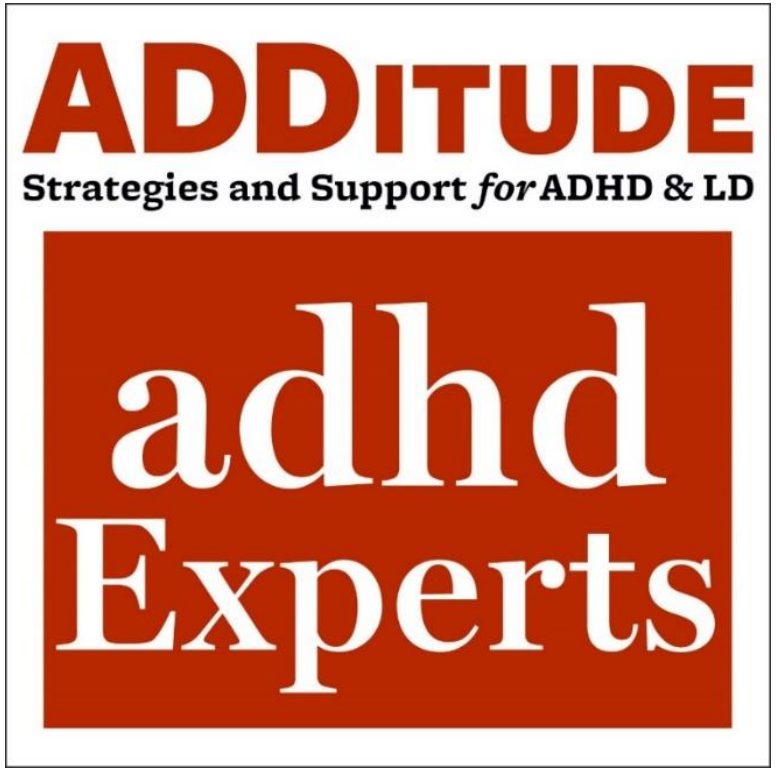

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Upcoming Webinars

- **Tuesday, March 4, 2025, at 1pm ET**

Living with ADHD: It's Different for Women
with Lotta Borg Skoglund, M.D., Ph.D., Andrea Chronis-Tuscano, Ph.D., Ellen Littman, Ph.D., Diane Miller, Psy. D., M.Ed., and Maggie Sibley, Ph.D.
https://www.additudemag.com/webinar/women-with-adhd-roundtable/

- **Tuesday, March 11, 2025, at 1pm ET**

A Parenting Toolkit for Moms and Dads with ADHD
with Christina Danko, Ph.D.
https://www.additudemag.com/webinar/parents-with-adhd/

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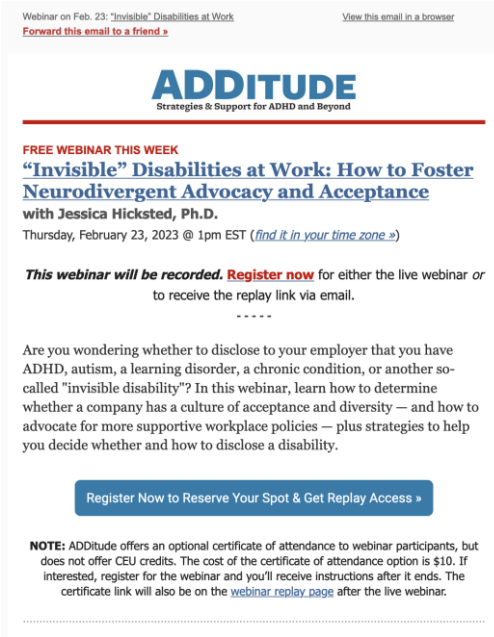

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FREE WEBINAR THIS WEEK

"Invisible" Disabilities at Work: How to Foster Neurodivergent Advocacy and Acceptance

with Jessica Hicksted, Ph.D.

Thursday, February 23, 2023 @ 1pm EST (find it in your time zone »)

This webinar will be recorded. Register now for either the live webinar *or* to receive the replay link via email.

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